Medicinrådet

Bilag til Medicinrådets anbefaling vedr. hydrokortison med modificeret udløsning (Efmody) til behandling af klassisk medfødt binyrebarkhyperplasi

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. hydrokortison med modificeret udløsning (Efmody)
2. Forhandlingsnotat fra Amgros vedr. hydrokortison med modificeret udløsning (Efmody)
3. Ansøgers endelige ansøgning vedr. hydrokortison med modificeret udløsning (Efmody)

a NEUROCRINE BIOSCIENCES® Company
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The Danish Medicines Council
Dampfærgevej 21-23, 3rd floor
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19 December 2022

Re: The Medicines Council's draft assessment regarding Efmody for the treatment of classic congenital adrenocortical hyperplasia (document number: 158644)

Diurnal regrets that Medicines Council has not recognised the evidenced clinical benefits of Efmody and clear unmet need for new treatment options for the Danish adolescent and adult patients with congenital adrenal hyperplasia (CAH).

Diurnal requests the Medicines Council to consider **restricted reimbursement for Efmody to those Danish adolescent and adult patients who are poorly controlled with the current treatment options**, more specifically Efmody reimbursement to be restricted to:

I. a second-line treatment option in adolescents not adequately controlled on maximum guideline doses of immediate-release hydrocortisone;
II. a third-line treatment in adults not adequately controlled on maximum guideline doses of immediate-release hydrocortisone and/or dexamethasone / prednisolone;
III. Efmody should not be used in CAH patients who are well controlled within guideline recommended doses.

Detailed feedback on the draft assessment report:

In general, the draft report does not provide a comprehensive presentation of supporting clinical evidence for Efmody, and it contains statements, which are not supported by evidence. Diurnal is happy to provide more detailed feedback and discuss further with the DMC and Diurnal's Chief Medical Officer to ensure data is interpreted and presented fairly and accurately.

Detailed feedback:

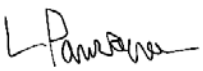
- Undertreatment results not only in high levels of androgen hormones, but also risk of adrenal crisis, which can be deadly without prompt emergency care.
- Diurnal is not aware of data supporting the statement regarding Danish patients having a better disease control: "The Medical Council assesses overall that the Danish patients experience better disease control than the patients in the study at baseline, with which the effect of Efmody may be less in Danish clinical practice than in study data." Therefore, Diurnal requests the DMC to present supporting evidence for this statement.
- There seems to be a misunderstanding on DIUR-006 treatment arm. Contrary to the DMC's interpretation, there is no hydrocortisone comparator arm in the DIUR-006 study as all patients received Efmody. Please ensure Efmody trial designs and data are presented accurately.
- It is contradictory to mention the European Society of Endocrinology recommendation which states that longer-acting glucocorticoids should not be used in children and adolescents due to adverse effect on growth, yet according to the DMC 10% of children and adolescents in Denmark are treated with dexamethasone (Table 1). Diurnal requests the DMC to comment on the use of dexamethasone in children and adolescents before cessation of growth.
- Section 1.6.1. DIUR-005: Please mention that the dose titration was blinded to minimise bias. In addition, please ensure comprehensive presentation of Efmody data. For example, the area under the 24-hour profiles curve (AUC) data, which is statistically significant is not provided in its completeness.
- Section 1.6.2. DIUR-006: Following statement is not correct: "The study was completed in April 2022, but the applicant has only included data up to the end of April 2020 in the application. In the original article, data up to the end of April 2019 is presented". The DIUR-006 study went through database lock in November 2022; hence, final CSR is not yet

available. Data from the latest data cut (third interim analysis) was submitted as part of the original reimbursement application, which was submitted to the DMC in May 2021. It has taken until December 2022 for the DMC to provide the assessment report. Diurnal is happy to submit the final data cut once final DIUR-006 CSR completed.

- Economic Section 1.7.1. According to the DMC, approx. 50% of Danish CAH patients are treated with dexamethasone, given in the evening, and the combination treatment, provides a better disease control. Dexamethasone is more potent than immediate-release hydrocortisone; hence, patients are often over-treated with dexamethasone. This is associated with several adverse effects, such as poor bone health, growth issues, cardiometabolic issues. In addition, taking a high dose of steroid late in the evening causes sleep disturbance, lack of sleep and an adverse metabolic profile. Downside of good androgen control in dexamethasone treated patients is overtreatment – Diurnal request the DMC to provide balanced presentation of downsides of use of dexamethasone in CAH patients.
- Please provide supporting reference for the following statement: "In the Danish patient population, around 75% of the patients will be in good disease control, and the Medical Council estimates that this entails further uncertainty and the risk of overestimating the expected effect in Danish clinical practice".
- It is incorrect to assume that Efmody is same as long-acting glucocorticoid. Efmody is the only hydrocortisone replacement therapy that provides physiological cortisol replacement due to its unique modified-release mechanism of action that allows physiological cortisol levels over 24-hour period. This is very different to cortisol replacement provided by long-acting glucocorticoids.
- Diurnal asks the DMC to be specific about what is the dexamethasone dose in HC dose equivalents used in their economic assessment.
- Table 1-5 Section 1.8.1. Please check spelling of Efmody throughout the report. Table is not complete as key data is missing, i.e. A4 AUC data is not included. Complete dataset should be used considering that 50% of Danish patients receive dexamethasone and 90% receive hydrocortisone. To conduct comparison correctly hydrocortisone prior therapy on Efmody should be match with those continuing on hydrocortisone and for this the dose of glucocorticoid at week 24 is 25mg/day. Please add reminder that in DIUR-005: "tight disease control to androgen levels was applied". Dose sparing was examined only in DIUR-006, not in DIUR-005.
- Table 1-7. Median doses instead of mean doses should be used because is median values are more appropriate in non-parametric data (as published in Merke et al. 2021).
- Table 1-8.: The analysis presented in disingenuous given that 50% of Danish patients take dexamethasone in addition to hydrocortisone. The median (hydrocortisone equivalent) dexamethasone dose is 40mg/day. Please specify exact doses used in Denmark.
- It is unclear why the DMC assumes that there are signs of undertreatment in DIUR-006 when patients remain well controlled and number of adrenal crisis was similar or lower than population estimates. As published by Merke et al. 2021, 80% of patients treated with Efmody were well controlled (specified as serum 17-OHP <36nmol/L at 9am), and there were no signs of undertreatment.
- Efmody's clinical benefits over glucocorticoids are clearly demonstrated in the key clinical studies. Therefore, Efmody does not the same clinical value as the glucocorticoids and consequently use of cost minimization analysis is not appropriate method to measure economic value of Efmody. Cost-utility analysis Diurnal submitted is the only appropriate way to capture Efmody's benefits derived from better disease control with lower steroid dose. Diurnal requests the DMC to consider the cost-utility analysis submitted.
- Diurnal applied conservative market share assumptions in the budget impact analysis because patients who are well controlled within guideline recommended doses should not be treated with Efmody. Hence, it is more realistic and appropriate to use conservative market share estimates in the budget impact analysis instead of 100% assumed by the DMC.

Diurnal is committed to working together with the DMC to provide access to Efmody to those Danish CAH adolescent and adult patients who are currently poorly controlled despite receiving above guideline-recommended steroid doses. Such CAH patients currently have no treatment options - Efmody would offer a much needed treatment alternative to improve their disease control and avoid adverse effects of steroid over-treatment.

Yours faithfully,



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Forhandlingsnotat

Dato for behandling i Medicinrådet	25. januar 2023
Leverandør	Diurnal
Lægemiddel	Efmody (hydrocortison)
Ansøgt indikation	Klassisk medfødt binyrebarkhyperplasi til voksne over 18 år

Forhandlingsresultat

Amgros har opnået følgende pris på Efmody (hydrocortison):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP	Forhandlet SAIP	Rabatprocent ift. AIP
Efmody (hydrocortison)	5 mg	50 stk.	1.125,56	[redacted]	[redacted]
Efmody (hydrocortison)	10 mg	50 stk.	2.251,11	[redacted]	[redacted]

Prisen er ikke betinget af Medicinrådets anbefaling.

[redacted]

Informationer fra forhandlingen

Leverandøren ønsker at gøre lægemidlet tilgængeligt for danske patienter. Derfor har de tilbudt en ubetinget rabat. Leverandøren oplyser, at de ikke har mulighed for at tilbyde en pris, der svarer til prisniveauet på komparatorerne.

Konkurrencesituationen

Tabel 2: Sammenligning af lægemiddeludgifter

Lægemiddel	Dosis	Styrker og pakningsstørrelse	Pakningspris, SAIP	Årlige lægemiddeludgifter, SAIP
Efmody (hydrocortison)*	22 mg dagligt	5 mg, 50 stk. 10 mg, 50 stk.	[redacted]	[redacted]
Hydrokortison "DAK"	20 mg dagligt	20 mg, 100 stk.	[redacted]	[redacted]
Prednisolon "DAK"	5 mg dagligt	5 mg, 100 stk.	[redacted]	[redacted]

*22 mg dagligt anvendt jfr. Medicinrådets vurderingsrapport. Lægemiddelomkostningerne er beregnet for vedligeholdelsesbehandling, da patienterne hurtigt opnår den gennemsnitlige dosis på 22 mg dagligt. 40 % af patienterne får 20 mg dagligt mens 60 % af patienterne får 25 mg dagligt, derfor angives der ikke et antal pakninger.

Status fra andre lande

Norge: Anbefalet[1]
Sverige: Ikke anbefalet[2] [redacted]
England: Ikke vurderet.

Konklusion

[redacted]

[1] https://nyemetoder.no/metoder/hydrokortison-efmody
[2] https://www.tlv.se/beslut/beslut-lakemedel/avslag-och-uteslutningar/arkiv/2021-12-17-efmody-ingar-inte-i-hogkostnadsskyddet.html

Application for the assessment of EFMODY® (hydrocortisone modified-release hard capsules) for treatment of congenital adrenal hyperplasia (CAH) in adolescents aged 12 years and over and adults

Submitted by Diurnal Europe B.V.

CH EU-DN-0004 (preparation date: 11 Oct 2021).

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1. Basic information

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Overview of the pharmaceutical	
Proprietary name	Efmody®
Generic name	Hydrocortisone modified-release hard capsules
Marketing authorization holder in Denmark	Diurnal Europe B.V.
ATC code	H02AB09
Pharmacotherapeutic group	Endocrinology, cortisol replacement therapy
Active substance(s)	Hydrocortisone
Pharmaceutical form(s)	Modified-release hard capsules for oral use
Mechanism of action	Efmody is an oral capsule formulation that consists of uniform multi-particulate beads, which have an inert core, a hydrocortisone (active ingredient) drug layer which and a delayed release enteric outer coat. Active ingredient, hydrocortisone, acts as glucocorticoid receptor agonists. Efmody is the first finished pharmaceutical product licensed as a treatment for adolescents and adults with CAH that, due to the modified-release mechanism of the active ingredient hydrocortisone, mimics the physiological circadian rhythm of cortisol levels day and night. Importantly, Efmody replicates the physiological overnight increase in cortisol, thereby preventing ACTH-driven early morning excess production of adrenal androgens. Efmody given twice daily replicates both the early morning increase in cortisol as well as daytime cortisol levels and thus provides effective avoidance of possible clinical problems of cortisol under- and overtreatment.

Overview of the pharmaceutical	
Dosage regimen	Efmody is available in doses of 5mg, and 10mg. Key dose information from the provisional draft Efmody SmPC, Section 4.2, provided below – please see the Danish SmPC for further information: *Treatment should be initiated by physicians experienced in the management of CAH.* *As maintenance therapy the dose must be individualised according to the response of the individual patient. The lowest possible dose should be used. Monitoring of the clinical response is necessary and patients should be observed closely for signs that might require dose adjustment, including changes in clinical status resulting from remissions or exacerbations of the disease, changes in electrolytes particularly hypokalaemia, individual responsiveness to the medicinal product, and the effect of stress (e.g. surgery, infection, trauma). As the treatment has a modified-release profile, blood tests are used to monitor clinical response, assessment of the evening dose should be done with a morning blood test and assessment of the morning dose should be done with an early afternoon blood test.* *During excessive physical and/or mental stress it may be necessary to increase the dose of Efmody, and/or add additional immediate release hydrocortisone especially in the afternoon or evening. Dose adjustments should be considered in case of concomitant use of potent CYP3A4 inducers or inhibitors.* *Recommended replacement doses of hydrocortisone are 10-15 mg/m2/day in adolescents aged 12 years and over who have not completed growth, and 15-25 mg/day in adolescents who have completed growth and adult patients with CAH. In patients with some remaining endogenous cortisol production a lower dose may be sufficient.* *At initiation the total daily dose should be split into two doses with two thirds to three quarters of the dose given in the evening at bedtime and the rest given in the morning. Patients should then be titrated based on their individual response.* *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.*
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Treatment of congenital adrenal hyperplasia (CAH) in adolescents aged 12 years and over and adults.
Other approved therapeutic indications	There are no other approved therapeutic indications.
Will dispensing be restricted to hospitals?	No. Efmody is expected to be approved with the dispensing group “AP4NB” which would mean that Efmody is either given free of charge at the hospital or prescribed by specialist physicians to the patient to be bought at the primary pharmacies.
Combination therapy and/or co-medication	No combination therapy, or co-medication needed for Efmody. Patients expected to take same co-medication as they are currently taking together with standard glucocorticoid treatment (cortisol replacement).
Packaging – types, sizes/number of units, and concentrations	One pack contains 50 capsules of: Efmody 5mg modified-release hard capsules. Efmody 10mg modified-release hard capsules. Please note that Efmody 20mg modified-release hard capsules will not be commercially availble in Denmark.
Orphan drug designation	No.

2. Abbreviations

Term/acronym	Definition
17-OHP	17-hydroxyprogesterone
21-OHD	21-hydroxylase deficiency
A4	Androstenedione
AC	Adrenal crisis
ACTH	Adrenocorticotropic hormone
ADHD	Attention-deficit hyperactivity disorder
AEs	Adverse events
AI	Adrenal insufficiency
ANCOVA	Analysis of Covariance
AUC	Area under the curve
BMD	Bone mineral density
BMI	Body mass index
BOI	Burden of illness
BSA	Body Surface Area
CAH	Congenital adrenal hyperplasia
CaHASE	Congenital adrenal Hyperplasia Adult Study Executive
C-CAH	Classic congenital adrenal hyperplasia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
CPRD	Clinical Practice Research Datalink
CRD	Core reimbursement dossier
CRH	Corticotropin-releasing hormone
CTX	C-terminal cross-linked telopeptide
CVD	Cardiovascular disease
DEXA	Dual-energy X-ray absorptiometry
DHEAS	Dehydroepiandrosterone sulphate
DSD	Disorders or differences of sex development
EES	Efficacy evaluable analysis set
ECG	Electrocardiogram
EMA	European Medicines Agency
EQ-5D	EuroQol-5D
EU	European Union
EUnetHTA	European Network for Health Technology Assessment
FAS	Full analysis set
FH	Final height
FH-Z	Final height Z-score
GC	Glucocorticoid
GH	Growth hormone

HADS	Hospital Anxiety and Depression Scale
HbA1c	Glycated haemoglobin
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
HPA	Hypothalamic pituitary adrenal
HR	Hazard ratio
HRQL	Health-related quality of life
hsCRP	High-sensitivity C-reactive protein
HSDS	Height standard deviation score
HTA	Health technology assessment
IA	Interim analysis
ICD-10	International Classification of Diseases 10
ICER	Incremental cost-effectiveness ratio
ICF	Informed consent form
ICU	Intensive care unit
ICH	International Council for Harmonisation
IECs	Independent Ethics Committees
IIEF	International Index of Erectile Function
IMP	Investigational medicinal product
IQR	Interquartile range
IR	Immediate-release
IRBs	Institutional Review Boards
ITC	Indirect treatment comparison
IWRS	Interactive Web Response System
LS	Least squares
MAF	Multidimensional Assessment of Fatigue
mg	Milligram
MHRA	Medicines and Healthcare Products Regulatory Agency
mmHg	Millimetres of mercury
MPH	Mid-parental height
MR	Modified-release
MRHC	Modified-release hydrocortisone
N	Number
N/A	Not applicable
NBS	Newborn screening
NC-CAH	Non-classic congenital adrenal hyperplasia
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NOS	Not otherwise specified
NR	Not reported
NS	Not significant
OR	Odds ratio
ORR	Overall response rate

PedsQL	Paediatric quality of life
PEM	Primary endpoint measure
PIL	Patient information leaflet
PGWB	Psychological general well-being
PRA	Plasma renin activity
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient-reported outcome
Pts	Patients
QALY	Quality-adjusted life year
QoL	Quality of life
SAS	Safety Analysis Set
SBP	Systolic blood pressure
SD	Standard deviation
SDS	Standard deviation score
SF-12	Short Form 12
SF-36	Short Form Health Survey Questionnaire – 36 item
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
sOB-R	Soluble leptin receptor
SV	Simple virilising
SW	Salt wasting
TART	Testicular adrenal rest tumour
TLR	Targeted literature review
ULN	Upper limit of normal
WHO	World Health Organization
WHO-QOL-BREF	World Health Organization Quality of Life Instruments
WMD	Weighted mean difference

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4. Summary

Congenital adrenal hyperplasia (CAH) is a rare condition caused by enzyme deficiency in cortisol biosynthesis. The condition is characterised by adrenal insufficiency and androgen excess.[3-5] Adrenal insufficiency causes life-threatening adrenal crises, while androgen excess causes atypical genitalia in neonates, promotes abnormal growth, short stature, and precocious puberty, and in adulthood, virilisation of women and infertility in both sexes.[3-5]
Treatment aims to replace cortisol, and, where necessary, aldosterone. However, current therapies are unable to replicate the diurnal rhythm of cortisol, and supraphysiological doses of glucocorticoids are typically needed to suppress adrenal androgens. Thus, management of CAH involves balancing glucocorticoid doses to avoid both glucocorticoid deficiency, risking life-threatening adrenal crisis, and iatrogenic glucocorticoid excess, leading to short stature, obesity, hypertension, osteoporosis, infertility in both sexes, and an adverse cardiometabolic profile.[6-10]
Notably, current glucocorticoid therapy also does not adequately replicate the physiological early morning cortisol release, which is necessary to control adrenal androgens prior to waking. This then creates a situation where the glucocorticoid medication taken by the patient after waking is too late to control the early morning androgen surge (i.e. the medication is always trying to catch-up with poor overnight control). Lack of androgen control in the morning drives usage of higher doses of glucocorticoids which causes well-characterised dose-dependent adverse outcomes.[4]
In Denmark, there is no standard of care for adult CAH, but immediate-release hydrocortisone remains the preferred treatment option over longer acting glucocorticoids prednisolone, and dexamethasone, or Plenadren (modified-release hydrocortisone tablets). For growing adolescents, immediate-release hydrocortisone is the recommended replacement therapy and Alkindi is the only approved and reimbursed option for paediatric CAH patients in Denmark (the other hydrocortisone preparations [10mg and 20mg tablets] are not specifically approved for paediatric CAH and no dosing guidance is provided for paediatric CAH in the SmPCs). Both adult and adolescent patients are treated with various dosages, formulations and complex regimens with unphysiological pharmacokinetics (1–4 times daily; reverse circadian dosing, and higher than recommended doses are used).[11, 13-15] Despite this, approximately two-thirds of patients are estimated to have poor disease control and patients are exposed to overtreatment with steroids resulting in a range of severe adverse outcomes and increased mortality.[4, 6-10]
Efmody is indicated for the treatment of adolescent (aged ≥12 years) and adult patients with CAH and is anticipated to replace current therapies to become the first-line treatment option for these patients in Denmark. The clinical trial programme , which included a Danish trial site, demonstrated that Efmody provides physiological cortisol replacement over 24 hours in CAH patients. The pivotal Phase III study (DIUR-005) failed to meet its primary endpoint of superiority in change from baseline to 24 weeks of the mean of the 24-hour standard deviations score (SDS) profile for androgen precursor 17α-hydroxyprogesterone (17-OHP). This is because the primary endpoint failed to capture the morning improvement in biochemical control on Efmody due to an intense titration protocol, which is not normal in routine clinical practice, log-transformation of the data and use of a mean over 24 hours resulting in a loss in the difference between the treatment groups. However, the raw data showed significant improvement of the clinically relevant endpoint of morning biochemical control, with reduced 24-hour area under the curve (AUC) and 17-OHP amplitude in patients receiving Efmody compared to those receiving standard glucocorticoid therapy.[16] Furthermore, the Phase IIIb DIUR-006 safety extension study demonstrated a clinically meaningful steroid-sparing effect of Efmody, leading to sustained biochemical control at a physiological dose. Both trials also demonstrated that Efmody was associated with fewer adrenal crises (compared to standard glucocorticoid therapy), stabilisation of weight gain and bone mineral density and, importantly, with patient-relevant endpoints including restoration of menstrual cycles, improved pregnancy and partner pregnancies and fewer uses of sick days rules. The safety of Efmody was consistent with the well-established long-term experience with hydrocortisone.
A *de novo* model was developed to assess the cost-effectiveness of Efmody for the treatment of CAH in adolescents (aged ≥12 years) and adults. The model consists of a series of sub-models investigating the impact of CAH on a number of associated co-morbidities (adrenal crises, obesity, fertility, height, diabetes, bone health and cardiovascular disease [CVD]) and their impact on cost, health-related quality of life and mortality. The modelling approach and some of the sub-models selected align with those used in the Alkindi (hydrocortisone granules in capsules for opening) cost-effectiveness model (adrenal crises, height, obesity and diabetes) that was the basis for the reimbursement approval

of Alkindi in Nordic countries (cost-effectiveness data was not submitted as part of the DMA Alkindi pricing and reimbursement submission; there was no DMC Alkindi reimbursement submission) and also with a published health burden model of CAH (adrenal crises, obesity, fertility, CVD and fractures).[17,18,149] The Efmody model quantifies the potential long-term benefit Efmody provides from both normalised cortisol and androgen levels throughout the day and night, and through reduction of overall steroid dose compared to current glucocorticoid therapies. The normalised cortisol and androgen levels resulting from Efmody are anticipated to negate the impact of uncontrolled androgens and unphysiological cortisol levels experienced by CAH patients receiving current therapies. Efmody provides this benefit while exposing patients to lower levels of steroids thereby reducing the risk of associated comorbidities. Therefore, for the majority of sub-models, the impact of both normalising cortisol and androgen levels, and reducing glucocorticoid dose were captured. This assumption was validated by seven European endocrinologists (including three Nordic endocrinologists) and extensive sensitivity analyses are included to address uncertainty. The clinical data for the glucocorticoid therapy and utility and cost data were taken from published sources. Resource use values were taken from published sources and assumptions made for Denmark where data could not be retrieved. The combined quality adjusted life year (QALY) impact of each of the sub-models is captured through the estimation of utility and mortality multipliers for each comorbidity.

Efmody is a clinically effective and cost-effective treatment option for CAH in adolescents (aged ≥12 years) and adults. Efmody is associated with an incremental gain of 3.57 QALYs per patient. This results in an ICER of DKK 76,276 at the list price. Efmody is expected to result in cost savings of resource use required to monitor CAH patients due to its simple and easy-to-monitor treatment regimen. Results also show that costs savings may arise from reduced hospitalisations due to fewer adrenal crises, reduced fertility interventions, reduced cardiometabolic burden (CVD and diabetes) reduced bone fractures and use of sick day (where patients need to increase their dose of medication to meet the natural demands on cortisol during illness and situations of stress) medication, leading to reduced resource use over a patient's lifetime. Extensive sensitivity analysis has been included in the model to address uncertainty.

Efmody is licensed for the treatment of adolescents (aged ≥12 years) and adults with the life-threatening rare condition of CAH. CAH is a predictable condition as new-born screening is used in Denmark and the incidence of CAH has been reported to be 1 in 10,000 live births but this includes non-classic CAH patients who are typically asymptomatic and require no life-long replacement therapy.[118] Incidence of classic CAH requiring life-long replacement therapy (hence classic CAH is the focus of this dossier; CAH is referring specifically to the classic CAH) is estimated at 1:14,000 live birth in Denmark. Due to small patient numbers, Efmody as a first-line treatment is expected to have a limited budget impact versus current standard care for treatment of both adolescents and adults.

5. The patient population, the intervention and choice of comparator(s)

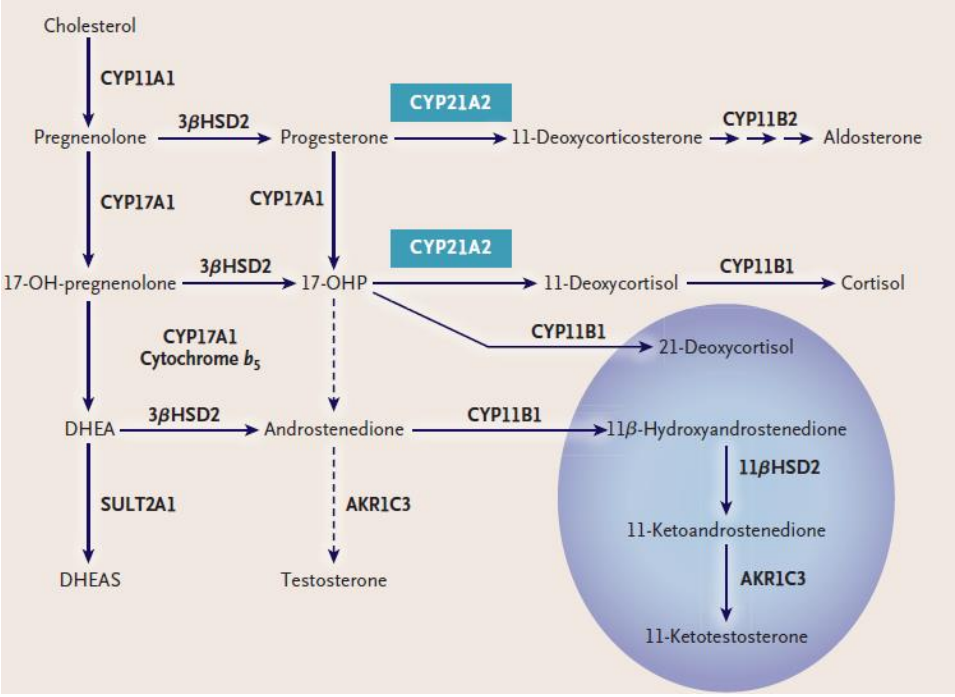
5.1 The medical condition and patient population

5.1.1 The medical condition

Congenital adrenal hyperplasia (CAH) is the overarching medical term for a group of rare genetic disorders that all arise from enzymatic defects in adrenal cortisol biosynthesis.[2, 3] Several enzymes are involved in the synthesis of the essential steroid cortisol. In CAH, the most commonly affected enzyme is 21-hydroxylase (resulting from a defect in the gene *CYP21A2*), which accounts for approximately 95% of all CAH cases.[2, 3,4] Thus, the term CAH is often synonymous with 21-hydroxylase deficiency (21-OHD). Congenital adrenal hyperplasia is a lifelong disease; hence, there are no specific age groups that are affected by the medical condition.

Cortisol is produced via a dynamic adrenal steroidogenesis process that comprises five major enzyme-mediated steps which are under hypothalamic-pituitary adrenal (HPA) axis control. Adrenal steroidogenesis, depending on the series of enzymatic steps taken, converts cholesterol to the glucocorticoid cortisol, the mineralocorticoid aldosterone, or the androgen testosterone (Figure 1).[4]

Figure 1: Pathways of adrenal steroid biosynthesis



Source: Merke et al. 2020[4]

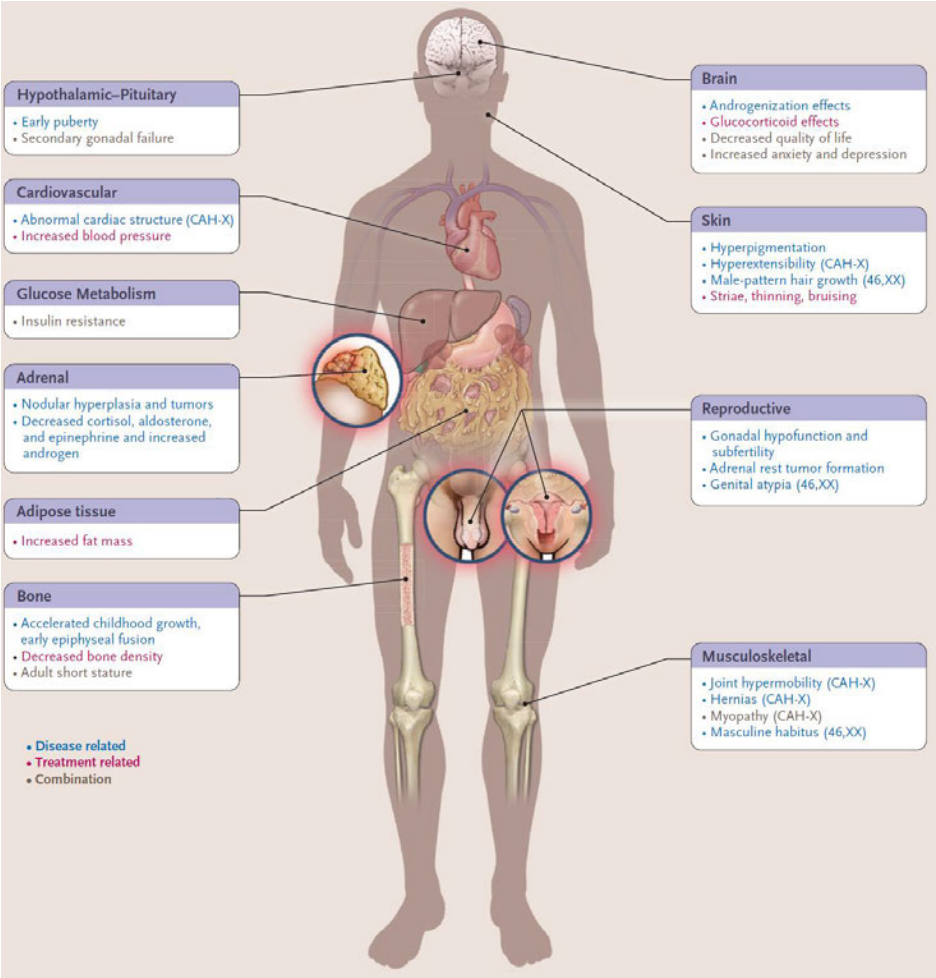
Conventionally, 21-OHD CAH is divided into classic 21-OHD CAH (either salt-wasting [SW] or simple virilising [SV] – this subtype requires daily cortisol replacement therapy; hence, CAH refers specifically to classic CAH in this dossier) and non-classic 21-OHD CAH (NC-CAH; this subtype rarely requires therapy and is not the focus of this dossier). Classic CAH is a complex and often debilitating disease, with an underlying pathophysiology of multiple hormonal imbalances.[2, 3] Cortisol biosynthesis is under HPA axis control and irregularities in its synthesis create an imbalance between cortisol and its precursor products; under HPA regulation, low or absent cortisol synthesis leads to increased androgen production and enlargement of the adrenal gland (hyperplasia).[2, 3] Consequentially, patients with CAH experience hyperandrogenism (always present), hypocortisolism (always present) and imbalanced aldosterone (dependent upon the nature and severity of the enzyme deficiency, commonly aldosterone deficiency).[2, 3] This underlying hormonal milieu and its treatment, is responsible for the wide-ranging, complex and often debilitating patient symptomatology and comorbidity profile of CAH.[2, 3] The cortisol deficiency, present since birth, leads to symptoms of adrenal insufficiency (AI) and places the patient at lifetime risk of life-threatening adrenal crises. In addition, androgen excess as well as suboptimal replacement treatment (i.e. with synthetic cortisol [glucocorticoids]) of CAH (either as inadequate dosing or supraphysiological dosing) underlie several adverse health outcomes including genital virilisation (in both females and males), precocious puberty, impaired growth, poor bone health, fertility issues, cardiometabolic events (including obesity and diabetes) and, as a consequence of exposure to supraphysiological dosing, iatrogenic Cushing Syndrome.[2] The culmination of all these adverse outcomes is that patients with CAH have an excess mortality risk compared to the healthy population.[5-8,70,71] Increased risk of mortality was demonstrated in a Swedish population-based national cohort study - Falhammar et al. 2014 studied patients with CAH (21-hydroxylase deficiency, n=588; *CYP21A2* mutations known, =80%), and compared them with controls (n= 58,800). Data were derived through linkage of national population-based registers. Mean age of death was 41.2 ± 26.9 years in patients with CAH and 47.7± 27.7 years in controls (p=0.001).[70] Among patients with CAH, 23 (3.9%) had died compared with 942 (1.6%) of controls. The hazard ratio (and 95% confidence interval) of death was 2.3 (1.2– 4.3) in CAH males and 3.5 (2.0 – 6.0) in CAH females. In addition, while the literature is either sparse (caregiver burden and economic burden) or conflicting (health-related quality of life [HRQL]), overall, CAH is associated with a substantial burden, particularly on caregivers who experience high levels of anxiety, depression and worry for their loved one.[9-11]

While the treatment of CAH implies a simple replacement of the missing cortisol, in practice treating CAH is more complex.[2, 12, 13] HPA regulation is diurnal in nature, which means cortisol is released in a circadian rhythm and has a short pharmacokinetic half-life. Replicating this physiological release with current glucocorticoid therapy (e.g. immediate-release hydrocortisone) over 24-hours is challenging. While current treatments have tried to mimic the

effects of physiological release of cortisol through various regimens (e.g. reverse circadian regimen), in practice many of the current treatments lead to peaks of supraphysiological cortisol levels followed by trough periods of hypocortisolism each day. The impact of inadequate replication of cortisol release with current glucocorticoid therapy can lead to androgen excess, androgen suppression and hypocortisolism. In addition, over the long-term, androgen excess in CAH is managed by supraphysiological dosing of glucocorticoids (to compensate for the lack of physiological cortisol profiles). The interplay between treatment and cortisol profiles adds to the complex patient symptomology and comorbidity profile of CAH as mentioned above.

Current glucocorticoid therapy for CAH includes hydrocortisone (immediate-release and Plenadren [modified-release hydrocortisone tablets indicated for adrenal insufficiency]), and longer acting and more potent prednisolone, and dexamethasone (used mainly in combination with hydrocortisone in Denmark).[4] In CAH, the absent overnight cortisol results in excess adrenocorticotropic hormone (ACTH) secretion, which in turn drives excess generation of adrenal androgens prior to waking. This then creates a situation where the glucocorticoid medication taken by the patient after waking under-compensates the overnight poor control (i.e the medication is always trying to catch-up with overnight poor control). Hence, there is no consensus on optimal treatment for adults with CAH and therapy is often given in multiple doses (1–4 times a daily) and in complex dosing regimens (such as circadian or reverse circadian dosing regimens). In growing children with CAH, maintenance therapy with hydrocortisone 10–15mg/m^2/day divided into 2 or 3 doses is recommended; notably, guidelines recommend against the use of long-acting potent glucocorticoid preparations in growing children because of the risk of growth suppression with these preparations.[4] Real-world evidence indicates there is a breadth of complex and multiple dose glucocorticoid regimens being used in the clinical management of CAH, often at doses higher than recommended by clinical guidelines.[14] In addition, the complexity of current treatment regimens is associated with non-adherence.[15] Of note, during illness and situations of stress (e.g. major surgery or trauma), all patients with CAH need to increase their dose of medication to meet the natural increased demand on cortisol (known as sick day rules/dosing).[4] However, multiple episode of increased glucocorticoid exposure from the sick day regimens (stress dosing) contributes to long-term adverse events.
Taken together it can be seen that an unmet need exists for a new glucocorticoid replacement therapy that can replicate the physiological release of cortisol day and night. Further, a replacement therapy is needed that can achieve disease control at a physiological dose, throughout the day and night. In addition, new therapies are needed that can offer more simple dosing schedules that are easy to understand, convenient, and that ultimately lead to improved patient adherence and compliance. It is also of note that a new treatment that can provide both control at lower dosing and reduce the burden of sick day rules usage, thereby avoiding excessive glucocorticoid exposure and its associated long-term adverse outcomes, will offer significant improvements to current patient care.
Unique disease-related and treatment-related features of CAH that contribute to the severity of the disease are summarised in Figure 2.

Figure 2: Disease-related and treatment-related features of CAH



Note: Disease-related manifestations are shown in blue, treatment-related manifestations are shown in red, and clinical manifestations related to both the disease and the treatment are shown in brown. CAH-X syndrome is characterized by features of CAH combined with features of the hypermobility-type Ehlers–Danlos syndrome.

Source: Merke et al. 2020[4]

5.1.2 Epidemiology

Since 2009, as part of screening for congenital metabolic diseases, newborns in Denmark have been screened for CAH by determining the level of 17-OHP which means that patients relevant for treatment should be included in the Danish registry. [131, 136] This screening is only designed to detect the most severe forms of the disease (i.e. classic CAH which is the focus of this dossier). The State Serum Institute (SSI) immediately reports screen-positive children to the local children's department who contact the parents for further investigations and start any treatment.[136]

Published data on prevalence of classic CAH in Denmark is sparse. According to SSI, CAH occurs in approximately 1 in every 10,000 newborn babies in Denmark (equal number of boys and girls).[118] However, this figure includes non-classical CAH patients who usually do not require cortisol replacement therapy as they are relatively asymptomatic due to only having a partial cortisol deficiency. There is variation in reported prevalence estimates between populations. Global prevalence of classic CAH was reported to be in the range of 1 in 11,000 – 19 000 in Sweden[137, 138, 139] Nermoen et al (2017) reported a prevalence of 1 in 16,000 newborn children in Norway.[140] The recently published data by Zetterström et al (2020) is an update on the CAH screening from Jan 2011 until Dec 2019 which reported an incidence of 1:11,200 of CAH in Sweden (92% of the detected cases had the classic form of CAH). However, the incidence of CAH in Sweden was found to be relatively high and therefore not directly applicable for Denmark.[138]

Based on the estimated prevalence of 1:14,000, the total number of CAH patients in Denmark from the age ≥12 years is approximately 364 patients – please see further details in Table 1.

There are no subgroups of patients for whom Emfody is likely to have a different level of efficacy and/or safety than anticipated for the entire population; hence, there is no specific subgroup selection. Patient number estimates provided in Table 1 consider the complete licensed indication of Efmody.

There is no evidence to suggest that the incidence and prevalence of CAH would have changed in the past 5 years in Denmark. That is why current (unchanged over period of time) incidence and prevalence estimates are used to estimate eligible patient numbers for the upcoming 5 years. Eligible patient numbers for the last 5 years have not been provided (Table 1).

Table 1: Estimated number of patients eligible for treatment with Efmody

Eligible patient population	Year 1	Year 2	Year 3	Year 4	Year 5
Current population in Denmark (≥12 years)	5,100,961				
Population growth in Denmark (0.4% annual growth)	1.000	1.004	1.007	1.011	1.014
Prevalence of CAH	364	364	365	366	368
Incidence of CAH	0	1	3	4	5
Total eligible patient population	364	365	368	370	373

Sources: Nermoen et al. 2010; Lundberg et al. 2017; Zetterström et al. 2020. Denmark statistics: https://www.statbank.dk/statbank5a/selectvarval/define.asp?PLanguage=1&subword=tabsel&MainTable=FOLK1A&PXSId=199113 https://www.worldometers.info/demographics/norway-demographics/

5.1.3 Patient populations relevant for this application

Patient group relevant for this application is the licensed patient population for Efmody: adolescents (≥12 years) and adults with CAH. Eligible patient population estimates are provided in Table 1.
Efmody is expected to be the first-line replacement treatment for the above mentioned licensed patient population. This is because all the current steroid / glucocorticoid treatments are not able to reproduce natural cortisol levels over 24-hour period and hence fail to control androgen excess. In attempt to bring androgens into better control it is often necessary to use higher doses of glucocorticoid therapy (supraphysiological dosing) or expose the patient to unphysiologically high levels of glucocorticoid replacement therapy in the late evening - both of these are associated with well-established adverse effects of steroid overdosing, such as poor bone health, metabolic issues and increased mortality. There are no specific subgroups considered in the application.

5.1.3.1 Adolescents and Efmody

As mentioned above, the marketing authorisation for Efmody is for treatment of adolescent (aged ≥12 years) and adult patients with CAH, based on the Efmody clinical trial programme conducted in adults aged ≥18 years. Although Efmody was originally intended to be licensed in adults only, the decision to include adolescents (aged ≥12 years) in the licence was agreed with the EMA in 2019 following completion of the Phase III DIUR-005 trial.
CAH manifests itself similarly in adolescents and adults in terms of patient symptomology and comorbidities and the mode of action of glucocorticoid replacement therapy is the same in both age groups. However, it is noted that it may be considered more challenging to treat adolescents due to the need to protect growth (with treatment guidelines recommending against the use of long-acting glucocorticoids in adolescents[11]). The validity of the use of the adult trial data to inform adolescent dosing was supported by development of a human physiologically-based pharmacokinetic (PBPK) model for Efmody, which indicated similar pharmacokinetics in the two populations. Thus, the modelling of dose exposure in adolescents is considered sufficient data to safely use Efmody in adolescents, as per the Efmody licensed indication.

Note: The anticipated clinical benefit of Efmody in adolescents was validated through interviews with seven European endocrinologists (including two Swedish and one Norwegian endocrinologists) and modelled in the cost-effectiveness model (validated by one Swedish endocrinologist) – see Section 8 for further details.

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

In CAH, the goal of treatment is two-fold:[11]

- To replace the missing cortisol (and aldosterone in some patients);
- To make sure androgen levels are controlled day and night with the lowest possible glucocorticoid dose.

As such, there are no formal treatment guidelines in CAH, with patients receiving replacement glucocorticoids daily as required throughout their lifetime. Furthermore, there is no standard treatment regimen in place in Denmark, nor Danish-specific treatment guidelines for treatment of CAH in adolescents and adults. However, the international CAH treatment guidelines endorsed by the European Endocrine Society are followed – see Section 5.2.2. for further information.[11] Current therapy for adolescent (aged ≥12 years) and adult patients with CAH in Denmark is individualised and includes a variety of generic glucocorticoid medicines, including immediate-release hydrocortisone, prednisolone and dexamethasone (used mainly in combination with hydrocortisone in adults only), which are more potent, longer acting glucocorticoids (Table 2 and Table 26).[12, 15] Also Plenadren, which is modified-release hydrocortisone formulation indicated for adrenal insufficiency, is used in some adult CAH patients.
Immediate-release hydrocortisone is the mainstay of replacement therapy in growing adolescent CAH patients, because long-acting potent glucocorticoid drugs have a negative impact on growth. Alkindi (immediate-release hydrocortisone granules in capsules for opening, Marketing Authorisation Holder: Diurnal Europe B.V.) is currently the only licensed and reimbursed (Danish Medicines Agency reimbursement decision granted in Apr 2019) hydrocortisone formulation that allow accurate low doses and dose adjustments in paediatric CAH patients in Denmark.
In adult CAH patients in Denmark, several regimens of short-acting and long-acting glucocorticoid formulations are used, alone or in combination with hydrocortisone. The importance correct drug selection and dosage is highlighted in treatment recommendations.[11] Treatment choice is informed by patient preference and varies over time as the needs of the patient changes; for example, for patients whose priority is improving their fertility, treatment is tailored towards improved disease control by increasing glucocorticoid dose which may come at the expense of symptoms associated with treatment escalation (e.g. weight gain and poor bone health). For older patients, the priority may be around managing their lifespan and reducing their cardiovascular risk, with clinicians then choosing regimens that meet these treatment objectives. Despite the variety of complex regimens and patient-led treatment approaches utilised in CAH, immediate-release hydrocortisone is the most common glucocorticoid treatment used to treat adult patients. Plenadren (modified-release hydrocortisone tablets indicated for AI) is used to treat some adult CAH patients in Denmark. There are different hydrocortisone regimens being used with three to four times per day dosing, or dosing with reversed circadian pattern with the larger dose taken at night when physiological cortisol levels are typically lowest causing sleep disturbance and adverse metabolic profile.[11, 39] None of these hydrocortisone regimens result in cortisol levels that are physiological over a 24-hour period, and often supraphysiological doses are used to control androgen excess.[4, 11, 73] If adequate disease control is not achieved, or the patient has poor medication compliance due to multiple daily dosing, more potent glucocorticoids, prednisolone or dexamethasone, are used. Based on the feedback from Danish clinical experts, prednisolone is used in few patients only while dexamethasone is used in combination with hydrocortisone as an evening dose to try to control early morning androgen rise. The issue with prednisolone and dexamethasone and current hydrocortisone treatments is that they all fail to replicate physiological circadian cortisol levels necessary for androgen control. Since both prednisolone and dexamethasone are significantly more potent steroids than hydrocortisone, patients are often treated with excessive doses with serious physical consequences, such as Cushing syndrome and weight gain. Importantly, none of the existing treatments allow continued physiological cortisol replacement from adolescence to adulthood. This is a limitation of current therapy in CAH as starting with a physiological replacement therapy at an early age and being able to continue with the same treatment regimen in adulthood can be expected to improve compliance and health outcomes.
It is anticipated that Efmody will replace current treatments to become the first-choice treatment option in adolescent and adult CAH, as it is the first modified-release hydrocortisone preparation for CAH that has been shown to mimic the physiological profile of cortisol day and night, and control of androgen excess without exposing patients to supraphysiological doses of glucocorticoids.[20]

Table 2: Current glucocorticoid treatment options for CAH in adolescents and adults, licensing status and dose recommendation in Denmark

Hydrocortisone product (manufacturer)	Licence status: Treatment of CAH in adolescents and adults	Dose recommendation for adolescents and adults
Alkindi 0,5 mg, 1 mg, 2 mg and 5 mg[153]	EMA PUMA license for replacement therapy of adrenal insufficiency in infants, children and adolescents (from birth to <18 years old)	Adolescents with CAH: 10-15 mg/m^2, usually divided into 3-4 four doses. Adults with CAH: No approved label.
Hydrocortisone 10mg tablets (Orion)[127]	National license for replacement therapy for children with CAH and children/ adolescents <18 years with AI[127] Indicated for adults and children aged 1 month to 18 years where a dose of 10 mg and tablet formulation is considered appropriate. Tablets are scored; can be divided into two equal halves (2x5mg dose). Doses <5mg are unlicensed.	Adults and adolescents with CAH: No specific dose recommendation
Hydrocortisone 10mg and 20mg tablets (Oripharm Generics)[128]	National license for replacement therapy for children with CAH and children and adolescents <18 years with AI [128] Both 10mg and 20mg tablets are scored, can be divided into two equal doses (5mg, and 10mg, respectively).	Adults and adolescents with CAH: No specific dose recommendation (only for emergency treatment).
Hydrocortisone 20mg tablets (Takeda)[142]	The approved label is: "conditions and diseases by which glucocorticoids are indicated." [142]	CAH: The daily dose is typically 30 to 36 mg/m2 body surface, of which 1/3 is given in the morning and 2/3 is given in the evening. Daily maintenance dose is 20 to 25 mg/m2 body surface.
Plenadren 5mg and 20mg tablets (Takeda)[150]	The approved label is: "treatment of adrenal insufficiency in adults." Indication does not include CAH.	AI: Plenadren is given as maintenance therapy. Oral replacement doses must be individualised according to the clinical response. A common maintenance dose is 20–30 mg per day, given once daily in the morning. No dosing recommendation for CAH as not included the indication.
Dexamethasone "Abcur", 1mg and 4mg [152]	The approved label is: "diagnostic test of pituitary and adrenal cortex function."	No specific dosing recommendation for CAH
Prednisolon "DAK", 5mg[151]	No specific indication for CAH, or AI.	No specific dosing recommendation for CAH. Substitution therapy: Adults: 5 mg in the morning and 50% of the morning dose in the evening. Children: typically 4-5 mg per m^2 body surface area.

Patients should be carefully monitored for signs that may require dose adjustment, including changes in clinical status due to improvement or impairment of the disease, individual drug response and the effect of stress (e g surgery, infections and trauma). In stress situations, it may be necessary to increase the dose temporarily (sick day rules). Clinically severely affected patients in crisis with hyponatraemia and hypercalaemia are treated initially with i.v hydrocortisone (Solu-Cortef i.v.). In adolescents with acute adrenal crisis, at least 100 mg (dose is controlled by body weight) is administered, and thereafter, 100-200 mg as infusion or intermittent injections are administered the first day. [11,116]

Mineralocorticoids (Fludrocortisone/Florinef) are generally taken orally together with hydrocortisone in salt-wasting form of CAH. Mineralocorticoid deficiency is independent from glucocorticoid deficiency; hence, there is no difference in the use of fludrocortisone in patients receiving Efmody compared to standard glucocorticoids, and this is not further described in this dossier.

5.2.1.1 Alkindi

Alkindi (immediate-release hydrocortisone granules in capsules for opening) is currently the only licensed hydrocortisone formulation that allow accurate low doses and dose adjustments in paediatric CAH patients. Treatment is three times daily and Alkindi is the only EMA approved hydrocortisone for children and adolescents with CAH that is also approved for general reimbursement (for the approved paediatric patient population) in Denmark. Alkindi is mainly used in newborn infants and younger children with AI/CAH, while there have been limited prescriptions in adolescents – use is mainly in adolescents with swallowing difficulties who cannot take tablets and those who need low doses, which cannot be accurately obtained with 10mg hydrocortisone tablets.
Further details around Alkindi for the treatment of adolescents with CAH can be found in the dossier submitted to the Danish Medicines Agency in 2018.[18]

5.2.1.2 Hydrocortisone tablets

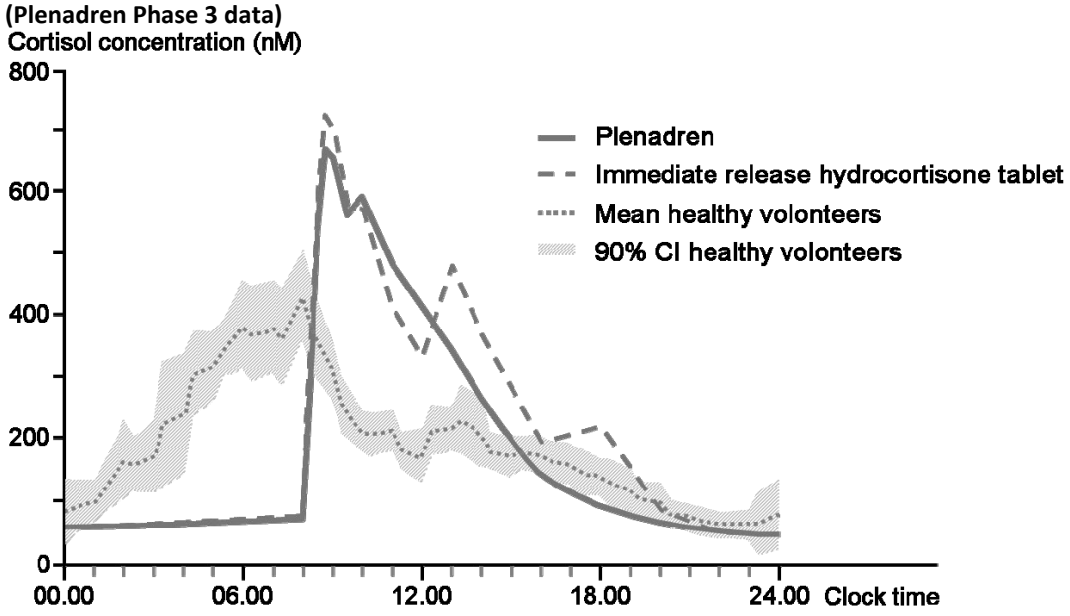
The approved license in Denmark for Hydrocortisone Orion is "substitution treatment for congenital adrenal hyperplasia in children" and "treatment of adrenal insufficiency in children and adolescents < 18 years". Congenital hyperplasia is not included in the licensed indication, nor dosing recommendation is provided for paediatric patients with CAH. Hydrocortisone Orion is indicated for adults and children aged from 1 month to 18 years where a dose of 10 mg and tablet formulation is considered appropriate. [127]

The approved license in Denmark for Hydrocortisone Takeda is "conditions and diseases in which glucocorticoids are indicated" [128] The lowest dose strength of current standard hydrocortisone for adults is 10mg which does not allow dose precision when doses lower than 10mg are needed by patients.

5.2.1.3 Plenadren – modified-release hydrocortisone tablets

Plenadren (modified-release hydrocortisone tablets, 5mg and 20mg, Shire) is indicated for treatment of AI in adults. Plenadren has a different pharmacokinetic profile to Efmody. Plenadren has an immediate-release with an extended duration profile [123], which is designed to allow patients with AI to dose once per day in the morning (Table 2 and Figure 3). This profile does not replace the normal overnight rise in cortisol and patients wake with a very low cortisol level (Figure 3). This lack of physiological replacement for overnight rise in cortisol levels by Plenadren, means it does not control the overnight rise in ACTH, which then continues to drive androgen secretion in CAH patients.

Figure 3: Plenadren Pharmacokinetic Profile compared to immediate release hydrocortisone and normal physiology (Plenadren Phase 3 data)



Source: Johannsson et al., 2012

A single published study where patients with CAH were treated with Plenadren did not report androgen results although these are both the causative agents of pathological effects and the gold standard for monitoring control of CAH.[124] Recent poster publications from an ongoing study with Plenadren suggested no improvement in androgen levels with several patients experiencing worse control [125] a finding similar to that in another poster report from Italy.[126] Furthermore, a study by Auer et al. (2021) showed that once-daily Plenadren cannot mimic physiological cortisol secretion in CAH and therefore fails in suppressing the nocturnal androgen surge, while Efmody controls overnight rise in 17-OHP.[74] In summary, the data showed no benefit over conventional therapy and Plenadren does not control androgen levels in the morning and requires the addition of standard glucocorticoid treatment to control CAH.

As evidence suggests Plenadren is sometimes used off-label (not as first-line treatment) in CAH patients, a feasibility assessment was undertaken to evaluate whether it is possible to conduct an ITC between Efmody and Plenadren in the treatment of adolescent (aged 12 years and over) and adult CAH. The conclusion is that ITCs cannot and should not be performed using the evidence currently available due to the following reasons:

- The publications for Plenadren are very limited
- There is limited data for baseline characteristics and demographics reported for Plenadren. Any comparison would be close to a naïve comparison across the studies with very low Plenadren - treated CAH patient numbers which would present a great potential for bias as study effects would remain embedded in the data
- The outcomes data for Plenadren is insufficient to use in any ITC analysis as there is no data for the primary and secondary outcomes of interest for Efmody

Overall, due to inadequacy of reporting of the Plenadren data in CAH patients, it is not feasible to perform any meaningful statistical comparisons between Efmody with Plenadren.

5.2.1.4 Prednisolone

The approved label for prednisolone does not mention AI or CAH as part of the indicated patient population.[151] Prednisolone is a medium-acting glucocorticoid preparation with a longer duration of action and has more potency than hydrocortisone. As it can have greater negative effect on growth it is only prescribed for adults with CAH. [11]

The glucocorticoid effect of Prednisolone corresponds to 3.5 to 5 times Hydrocortisone. Prednisolone is administered two times daily and is available as 2.5 mg and 5 mg tablets.

According to feedback from a Danish clinical expert, Prednisolone is prescribed to approx. 3% of adult CAH patients (See Section 8).

5.2.1.5 Dexamethasone

The approved indication for dexamethasone is “diagnostic test of pituitary and adrenal cortex function”, but AI or CAH are not mentioned as part of the indicated patient population.[152]

In Denmark, dexamethasone is mainly used in adult CAH patients in combination with hydrocortisone as an evening dose in attempt to control excessive morning androgen levels. Dexamethasone is not prescribed for adolescents with CAH because longer duration of action and increased potency compared to hydrocortisone can have a negative effect on growth. It has been estimated that growth-suppressive effect of dexamethasone may be up to 70- to 80-fold more potent than hydrocortisone.[11]

Dexamethasone is available as 1 mg (and 4 mg) tablets. The glucocorticoid effect corresponds to 25-50 times the hydrocortisone.[122] In adults, Dexamethasone is usually given in doses of 0.5 to 10 mg daily, depending on the condition being treated and there are no specific dose recommendations for CAH. According to FASS, the excretion of dexamethasone is approximately the same for children and adults if the dosage is adjusted with respect to their body area. Dosage should be planned for possible effects on growth and development as well as signs of adrenal suppression. [127]

5.2.2 Treatment guidelines

The current accepted international guidelines for management and treatment of CAH were developed by the (US) Endocrine Society and are endorsed by the European Society of Endocrinology and European Society for Paediatric Endocrinology (Table 3). These guidelines are the main treatment reference in Denmark as there are no Danish treatment guidelines for CAH.

As mentioned above, in CAH, the goal of treatment is two-fold:

- To replace the missing cortisol (and aldosterone in some patients);
- To make sure androgen levels are controlled day and night with the lowest possible glucocorticoid dose.

Details of the recommendations given by the international guideline are summarised in Table 3. In brief, the Endocrine Society guideline recommends that:

- In growing children with CAH, maintenance therapy with hydrocortisone 10–15mg/m^2/day divided into two or three doses is recommended.
- For the treatment of growing individuals with CAH, guidelines recommend against the use of long-acting potent glucocorticoid preparations, because of the risk of growth suppression with these preparations.
- In adults with CAH, there is no consensus on optimal treatment. Daily hydrocortisone and/or long-acting glucocorticoids as replacement therapy are recommended, but hydrocortisone is the preferred treatment.

The Endocrine Society guidelines[11] advocate the development of new treatment approaches that minimize the daily glucocorticoid dose with the goals of achieving physiological cortisol replacement and preventing excessive androgen secretion as normal adrenocortical secretion has a circadian rhythm and this is not replicated by none of the currently available treatment options. These are met by Efmody as described in Section 7.

Table 3: The Endocrine Society Clinical Practice Guidelines for CAH

Citation and hyperlink	Guideline summary
Speiser *et al.* 2018. Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*; 103: 4043–4088. https://academic.oup.com/jcem/article/103/11/4043/5107759	**Key recommendations (for classic CAH only)** Treatment of CAH • In growing individuals with CAH, we recommend maintenance therapy with hydrocortisone • In growing individuals with CAH, we recommend against the use of oral hydrocortisone suspension and against the chronic use of long-acting potent glucocorticoids • In adults with CAH, we recommend using daily hydrocortisone and/or long-acting glucocorticoids plus mineralocorticoids, as clinically indicated • In all individuals with CAH, we recommend monitoring for signs of glucocorticoid excess, as well as for signs of inadequate androgen normalisation, to optimise the adrenal steroid treatment profile • In all individuals with CAH, we recommend monitoring for signs of mineralocorticoid deficiency or excess • In women with CAH who become pregnant we recommend continued pre-pregnancy doses of hydrocortisone/ prednisolone and fludrocortisone therapy, with dosage adjustments if symptoms and signs of glucocorticoid insufficiency occur • In women with CAH who are pregnant, or trying to become pregnant, we recommend against using glucocorticoids that traverse the placenta, such as dexamethasone Stress dosing • In all patients with CAH who require glucocorticoid treatment, for situations such as febrile illness (>38.5°C), gastroenteritis with dehydration, major surgery accompanied by general anaesthesia, and major trauma we recommend increasing the glucocorticoid dosage • In patients with CAH under everyday mental and emotional stress and minor illness and/or before routine physical exercise we recommend against the use of increased glucocorticoid doses Monitoring treatment • In adults with CAH we recommend monitoring treatment through consistently timed hormone measurements relative to medication schedule and time of day • In adults with CAH we recommend that clinicians do not completely suppress endogenous adrenal steroid secretion to prevent adverse effects of over treatment
Key: CAH, congenital adrenal hyperplasia; C-CAH, classic congenital adrenal hyperplasia.	

5.2.3 Choice of comparator(s)

5.2.3.1 Pivotal Phase III DIUR-005 clinical trial

Selection of comparators in the pivotal Phase III trial DIUR-005 was based on standard glucocorticoids used as maintenance therapies in adult CAH patients - DIUR-005 had eleven study sites in 7 countries: 1 in Denmark, 2 in France, 1 in Germany, 1 in the Netherlands, 1 in Sweden, 4 in UK, 1 in USA.

5.2.3.2 Cost-effectiveness analysis

Selection of comparators in the cost-effectiveness model was done based on publications and feedback from Danish clinical experts on currently used glucocorticoid treatments in adolescents and adults with CAH in Denmark.

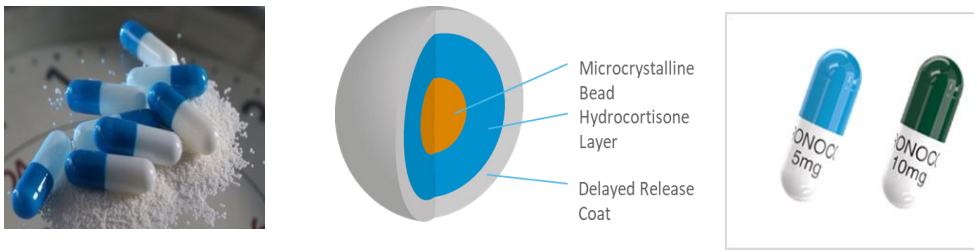
5.2.4 Description of the comparator(s)

Description of the comparators is provided in Sections 5.2.1. and 7.1.3. and 8.2.2.2.

5.3 The intervention

Efmody has been developed for the treatment of CAH.[21] Efmody consists of uniform multi-particulate beads, which have an inert core, a hydrocortisone (active ingredient) drug layer and a delayed release enteric outer coat contained within hard gelatine capsules (Figure 4).

Figure 4: Efmody: Modified-Release Hydrocortisone

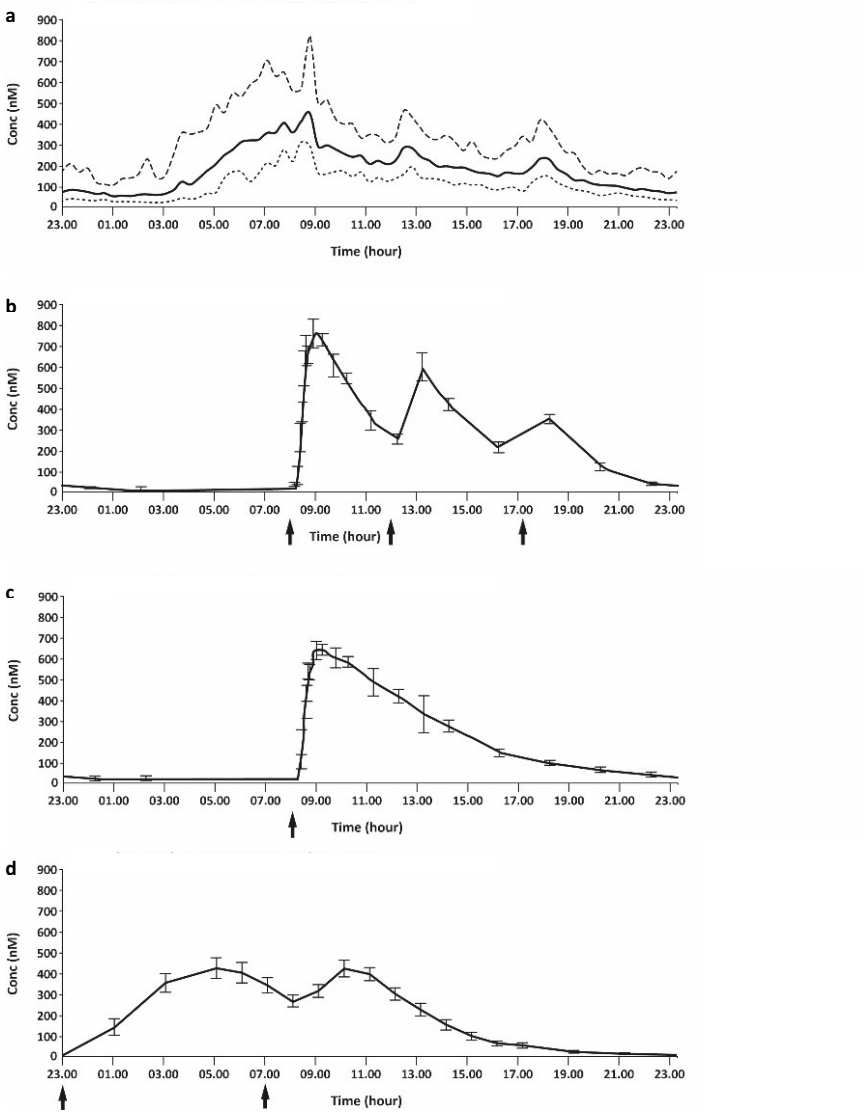


Source: Merke 2020.[22]

Efmody is available as a 5mg and 10mg capsule for oral use. The dose must be individualised based on the patient response and the lowest dose must be used. For the treatment of adolescents (aged ≥12 years) with CAH who have not completed growth, the dose of Efmody is 10–15mg/m^2/day. For adolescents who have completed growth and adult patients with CAH, the dose is 15–25 mg/day.[21]

Efmody aims to replace physiological cortisol concentrations by dosing in a twice-a-day simplified regimen; that is, at morning and night, such that the night-time dose provides a release of hydrocortisone in the early hours of the morning, providing a pre-waking rise in cortisol levels (see fourth [d] image in Figure 5). In this way, Efmody provides a similar cortisol rhythm and early morning peak to physiological control concentrations observed in healthy volunteers (compare fourth [d] image to first [a] image in Figure 5). Mimicry of the physiological cortisol profile is achieved by a delayed release and sustained absorption profile, such that when Efmody is administered at night (approximately 23:00 hours) there is a period of absence of drug release followed by a period of sustained absorption. This leads to elevation of the serum cortisol concentration in line with the normal circadian profile and corresponds to a peak cortisol concentration occurring in the morning (approximately 06:00-08:00 hours) (fourth [d] image in Figure 5).[20, 23] Importantly, the action of Efmody is closer to the natural physiology of cortisol release than immediate-release hydrocortisone and Plenadren as both of these comparators fail to mimic the circadian rhythm of cortisol (second [b] and third [c] image in Figure 5).

Figure 5: Efmody mimics physiological cortisol release



Notes: Diurnal cortisol concentration in a) healthy volunteers (mean, 10th and 90th centile) b) three times daily immediate-release hydrocortisone (mean and 95% CI) c) once daily Plenadren (mean and 95% CI) and d) twice daily Efmody (mean and SEM)
Key: AI, adrenal insufficiency; CI, confidence interval; CAH, congenital adrenal hyperplasia; SEM, standard error of the mean.
Source: Figure adapted from Porter *et al.* 2017.[23]

It should be noted that replicating the early morning cortisol rise in CAH is important for disease control, as the missing overnight cortisol (due to suboptimal treatment) results in excess early morning generation of adrenal androgens. Hyperandrogenism is responsible for part of the symptomology experienced by patients with CAH. In addition, clinical practice often involves supraphysiological doses of glucocorticoids to control the early morning androgen excess in CAH, further exacerbating the patient symptomology and comorbidity profile. Other issues with current treatments include their inability to mimic the effects of physiological release of cortisol, despite availability of various regimens, e.g. standard glucocorticoid therapies taken late at night do not address this problem – the patient is exposed to night time corticosteroid at a time when physiological levels are low, resulting in poor sleep and adverse cardiometabolic impact, in addition by the time the glucocorticoid is needed to suppress ACTH, the levels are too low.[24-26] As a result of this failure to mimic physiological cortisol release, the absent overnight cortisol in CAH results in excess ACTH secretion, which in turn drives excess generation of adrenal androgens prior to waking. This then creates a situation where the glucocorticoid medication taken by the patient after waking under-compensates the overnight poor control (i.e. the medication is always trying to catch-up with overnight poor control). Thus, the closely mimicked physiological release of cortisol offered by Efmody provides a normalised androgen profile in CAH and subsequent improvement in patient symptomology.[20, 23, 27]

The features of Efmody and dosing recommendations are summarized in the Table 4 and Table 5.

Table 4: Product features of Efmody

Non-proprietary name	Hydrocortisone modified-release hard capsules
Proprietary name(s)	Efmody
Marketing authorisation holder	Diurnal Europe B.V.
Class	Corticosteroids for systemic use; plain; hydrocortisone (cortisol)
Active substance(s)	Hydrocortisone
Pharmaceutical formulation(s)	Modified-release hard capsules for oral use
ATC code	H02AB09
Mechanism of action	Hydrocortisone is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastro-intestinal tract.
Indication	Efmody is indicated for the treatment of CAH in adolescents aged 12 years and over and adults
Contra-indications and warnings	**Contraindications** Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 of the SmPC. **Warnings** • Adrenal crisis • Pre-operatively, during serious trauma or during intercurrent illness • Infections • Immunisation • Undesirable effects of cortiocosterid replacment therpay • Gastric emptying and motility disorders • Growth retardation • Accelerated sexual maturation • Visual disturbance
Drug interactions	Efmody may interact with *CYP3A4* inducers, requiring a potential increase in Efmody dosing, including (but not limited to): • Anticonvulsants: phenytoin, carbamazepine and oxcarbazepine • Antibiotics: rifampicin and rifabutin • Barbiturates including phenobarbital and primidone • Antiretroviral medicinal products: efavirenz and nevirapine • Herbal medicines such as St John's Wort Efmody may interact with *CYP3A4* inhibitors, requiring a potential decrease in Efmody dosing, including (but not limited to): • Anti-fungals: itraconazole, posaconazole, voriconazole • Antibiotics: erythromycin and clarithromycin • Antiretroviral medicinal products: ritonavir • Grapefruit juice • Liquorice The desired actions of hypoglycaemic drugs including insulin are antagonised by corticosteroids.
Source: Efmody SmPC[151]	

Table 5: Administration and dosing of Efmody

Method of administration	**Dosing**
Doses	Dose available: 5mg and 10mg per capsule (**Note**: the 20mg per capsule dose is not commercially available)

Method of administration	Dosing
	Dosing strategy: Efmody is given as maintenance therapy. Dosage must be individualised according to the response of the individual patient. The lowest possible dosage should be used. As Efmody has a modified-release profile, blood tests are used to monitor clinical response. Assessment of the evening dose should be done with a morning blood test and assessment of the morning dose should be done with an early afternoon blood test. Replacement therapy for CAH Adolescents with CAH aged 12 years and over who have not completed growth:10-15mg/m^2/day Adolescents who have completed growth and adult patients with CAH: 15–25 mg/day Changing from conventional oral glucocorticoid treatment to Efmody When changing patients from conventional oral hydrocortisone replacement therapy to Efmody, the identical total daily dose should be given, but the dose should be given in two doses with 2/3 to 3/4 of the dose given in the evening at bedtime and the rest given in the morning. When changing patients from other glucocorticoids to Efmody an appropriate conversion factor should be used, and the patient monitored for response carefully. A starting dose exceeding 40mg per day of Efmody is not recommended. During serious trauma, intercurrent illness or periods of stress Dose adjustments may be necessary depending on the severity of the situation (as described below under dose adjustments below)
Dosing frequency	At initiation the total daily dose should be split into two doses with 2/3 to 3/4 of the dose given in the evening at bedtime and the rest given in the morning. Patients should then be titrated based on their individual response. 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.
Average length of a course of treatment	Anticipate continuous/lifelong treatment
Dose adjustments	Treatment should be initiated by physicians experienced in the management of CAH. Monitoring of the clinical response is necessary and patients should be observed closely for signs that might require dose adjustment, including changes in clinical status resulting from remissions or exacerbations of the disease, changes in electrolytes particularly hypokalaemia, individual responsiveness to the medicinal product, and the effect of stress (e.g. surgery, infection, trauma). As the treatment has a modified-release profile, blood tests are used to monitor clinical response, assessment of the evening dose should be done with a morning blood test and assessment of the morning dose should be done with an early afternoon blood test. During excessive physical and/or mental stress it may be necessary to increase the dose of Efmody, and/or add additional immediate release hydrocortisone especially in the afternoon or evening. In severe situations, an increase in dose is immediately required and oral administration of hydrocortisone must be replaced with parenteral treatment (see section 4.4 of Efmody SmPC). In less severe situations when parenteral administration of hydrocortisone is not required, during periods of physical and/or mental stress, additional immediate release hydrocortisone at the same total daily dose as Efmody should be given in three divided doses; Efmody should be continued as well with the usual regimen (i.e. a doubled daily dose of hydrocortisone) to allow for easy return to the normal replacement dose of Efmody once additional hydrocortisone is no longer required. In case of long-term increases in hydrocortisone daily dose due to prolonged periods of stress or illness, the additional hydrocortisone should be carefully weaned off.
Need for diagnostic or other tests	Diagnosis of CAH is through newborn screening (NBS) programmes, which means generally CAH cases are diagnosed soon after birth.

Method of administration	Dosing
	Given the nature and complexity of the disease, CAH patients are regularly monitored for disease control and effects of overdosing (approx. 3-monthly visits for paediatric and 6-monthly visits for adult CAH patients). Hence, introduction of Efmody does not change the need for diagnosis (treatment starts at age of 12 years) and disease monitoring, but Efmody is expected to make disease monitoring easier and less burdensome for the patient and healthcare provider.
Source: Efmody SmPC[151]	

5.4 Impact to clinical practice and place in the current treatment algorithm

Efmody is expected to be the first-line replacement therapy in adolescents and adults with CAH. This is because Efmody is the first modified-release capsule hydrocortisone preparation for CAH and is proven to replicate the physiological profile of cortisol over 24-hour period as described above, and to provide superior androgen control with a clinically relevant daily steroid dose reduction.[16] The pharmacokinetic profile of Efmody mimics the physiological circadian rhythm of cortisol, which cannot be achieved with immediate-release or long-acting glucocorticoids (Figure 5) and highlighted as an urgent unmet need in CAH therapy by the international CAH treatment guidelines (please see Section 5.2.2. for further information). Overall, the following clinical characteristics of Efmody treatment: delayed-release effect mimicking physiological circadian rhythm, twice daily dosing, glucocorticoid sparing effect, were considered of added clinical values for CAH patients by the CHMP when granting Marketing Authorisation warranting Efmody's place as first-line treatment for adolescents and adults with CAH.

Efmody offers additional benefit in adolescents with CAH, a life stage considered especially challenging to treat. Excess androgens from poorly controlled CAH and excessive doses of glucocorticoid therapy both lead to growth suppression.[4,40] Guidelines recommend only hydrocortisone in this patient group to avoid the risk of excessive doses.[11] In addition, clinicians strive to normalise pubertal development, which is also driven by excess androgens. The physiological cortisol replacement offered by Efmody is expected to reduce risk of excessive doses in adolescents while maintaining androgen control, thus protecting growth and pubertal development.

Many clinicians report that compliance is poor in the patient population and transition from paediatric to adult clinics is associated with patients disengaging from specialist care with the risk of loss of disease control and accumulation of future risks to fertility, cardiometabolic and bone health and adrenal crisis. The twice daily treatment regimen may help with compliance in this patient group. The medicine is taken last thing at night and first thing in the morning, avoiding the stigma of taking medication during the school / college day.

Lastly, Efmody is anticipated to make transition from paediatric to adult care easier, as patients can continue on Efmody.

6. Literature search and identification of efficacy and safety studies

Efficacy and safety of Efmody was directly compared to relevant comparators, current standard glucocorticoids, in the pivotal Phase III trial (RCT DIUR-005 – described in detailed in Section 7). In addition, based on a clinical systematic literature review (SLR), only one RCT, Efmody Phase III DIUR-005 trial, was identified that investigated the treatment of CAH in adolescents (aged 12 years and over) and adult patients. Full citation for the main reference (i.e. the only RCT indentified in the SLR) is: "Merke DP, Mallappa A, Arlt W, et al. Modified-release Hydrocortisone in Congenital Adrenal Hyperplasia. J Clin Endocrinol Metab. 2021".[16] Given that literature search did not provide further relevant documentation on the effect and safety of Efmody and the current standard glucorticoids, search and findings are not prescribed in Section 6. Clinical SLR report is provided in Appendix A.

7. Efficacy and safety

7.1 Efficacy and safety of Efmody compared to standard glucocorticoids for adolescent (≥12 years) and adult CAH patients

7.1.1 Relevant studies

The pivotal Phase III DIUR-005 study, and the long-term safety extension Phase IIIb DIUR-006 study, provide key evidence of the clinical benefits of Efmody for the treatment of adolescent (aged ≥12 years) and adult patients with CAH. These studies are summarised in Table 6.
DIUR-005 and DIUR-006 had eleven study sites in 7 countries: 1 in Denmark, 2 in France, 1 in Germany, 1 in Netherlands, 1 in Sweden, 4 in UK, 1 in USA.

Table 6: DIUR-005 and DIUR-006 – study summaries and data sources

	DIUR-005	**DIUR-006**
Trial design	Phase III Randomised Open-label At 4 and 12 weeks, dose titrations were made for both treatment groups, using identical rules, following centralized advice by 2 independent physicians blinded (blinded titration) to all data except 24-hour hormone profiles and an investigator-completed adrenal insufficiency checklist. Local investigators and patients were aware of the trial-group assignment but were otherwise blinded.	Phase III Open-label Single arm Extension study
Trial population	Adult (≥18 years; both genders) patients with C-CAH	Patients completing studies DIUR-005 and DIUR-003
Trial intervention	Efmody (development name Chronocort)	Efmody (development name Chronocort)
Trial comparator	Standard GC therapy (hydrocortisone, prednisone, prednisolone, dexamethasone)	Not applicable
Trial outcomes	Primary outcome measure (PEM): Change from baseline to 24 weeks of the mean of the 24-hour SDS profile for 17-OHP (disease control assessment) Secondary outcomes: PEM repeated for A4, further analyses of disease control (including post-hoc analyses), total daily dose of Efmody, body composition (DEXA), laboratory markers of interest (including bone turnover), QoL, and safety Exploratory outcomes: Partial AUC of 17-OHP, primary endpoint measure evaluated for the purposes of titration, changes relative to standard glucocorticoid therapy Key post-hoc analyses: Change in amplitude of the 17-OHP, log-transformed AUCs for 17-OHP and A4, percentage of patients with good disease control	Primary outcome: safety and tolerability of Efmody Secondary outcomes: disease control (assessed via 17-OHP and A4), total daily dose of Efmody, body composition, laboratory markers of interest (including bone turnover) and QoL Exploratory outcomes: Changes compared to pre-Efmody baseline at each visit in select parameters Key post-hoc analyses: rate of adrenal crises, good disease control, total daily dose, and absolute changes in select parameters
Published data sources	Merke *et al.* 2021 (primary manuscript)[16] Merke 2020 ENDO presentation[22]	

	DIUR-005	DIUR-006
Unpublished data sources	DIUR-005 Clinical Study Report[28] Data on File[29]	DIUR-006 Clinical Study Report[30] Data on File[29]
Key: A4, androstenedione; 17-OHP, 17-hydroxyprogesterone; AUC, area under the curve; C-CAH, classical congenital adrenal hyperplasia; DEXA, dual energy X-ray absorptiometry; GC, glucocorticoid; QoL, quality of life; SDS, standard deviation score.		

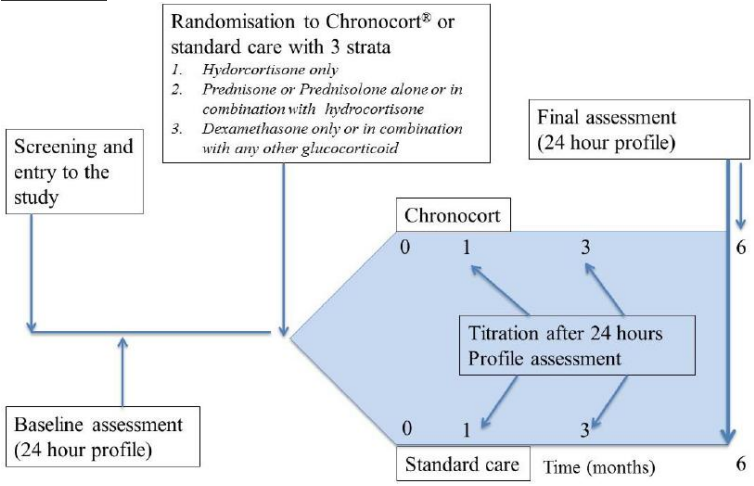
An overview of DIUR-005 and DIUR-006 study methodology is presented below (Section 7.1.2, Table 7, and Table 8). Full details of the trial methods, including all endpoints and methods of analysis, can be found in Appendix B.
Note: DIUR-005 is a completed study and the data cited in this submission are from the final CSR dated 30 Jul 2019 which had a final database lock of 14 Sept 2018. The DIUR-006 study is ongoing (expected to finish in the first half of 2022), the data cited in this submission for DIUR-006 are from the third interim analysis, with a data cut-off date of 30 Apr 2020 (DIUR-006 CSR dated 15 Dec 2020). The reporting period for this interim analysis 3 is 18 Aug 2016 to 30 Apr 2020. Merke et al. 2021 publication included data from the previous DIUR-006 interim analysis (Second interim analysis 18 Aug 2016 - 30 Apr 2019).

7.1.2 Trial overview and study objectives

As shown in Table 7, DIUR-005 was a Phase III, parallel group, randomised, open-label study. The study design of DIUR-005 is shown in Figure 6.

Figure 6: DIUR-005 study design

DIUR-005



Note: The developmental name of Efmody was Chronocort, which is how it was referred to in the final CSR. As such, this figure refers to Efmody as Chronocort (as it is sourced from the DIUR-005 CSR)
Source: Figure 1. DIUR-005 Final CSR (dated 30 Jul 2019).[28]

An overview of DIUR-005's objectives is presented in Table 7. In this trial, the assessment of disease control was measured by assessment of the biomarkers for androgen precursor 17-OHP and androstenedione (A4, 'sex' androgen - precursor for testosterone), both of which are established in the diagnosis and monitoring of CAH.[11] However, clinicians note that getting these markers into the normal (i.e. reference) range risks oversuppression and exposes the patient to unnecessarily high glucocorticoid levels. For this reason, clinicians target an optimal range for 17-OHP. Optimal biochemical control is defined as 17-OHP <3X the upper limit of normal (ULN); i.e. <36 nmol/L (<1,200 ng/ml) and A4 within the reference range. High concentrations of 17-OHP and A4 (standard ranges differ depending on whether the patient is in adolescence) indicate undertreatment. Titration of the dose should be aimed at maintaining 17-OHP concentrations below 36 nmol/L and A4 concentrations below 6.94 nmol/L.[8, 10, 31]
The primary endpoint measure (PEM) of DIUR-005 was the change from baseline to 24 weeks in the mean of the 24-hour 17-OHP standard deviation score (SDS). Natural log transformation was performed to approximate a normal distribution; for each 2-hourly value of log 17-OHP, the number of standard deviations from the midpoint of the natural logarithm of the reference range (males, 1.2–6.7 nmol/L [40–220 ng/dl]; females 1.2–8.6 nmol/L [40–285

ng/dl]) was calculated unsigned to provide equal weight to values above or below the midpoint (where 'sign' is the direction of deviations from the reference range); that is, the SDS profile was calculated as the SDS of log-transformed 17-OHP concentration unsigned since it was thought that this was the best way to account for both under- and over-treatment as both are considered equally undesirable outcomes. Thus, the PEM was chosen as a way of assessing better androgen control considered to be less variability around the midpoint of the reference range (see Appendix B). The use of SDS is commonly seen in relation to factors such as growth (where both growth failure and growth excess are clinically important), but in DIUR-005 it was chosen as a way of taking both under- and over-treatment into account.

Other study objectives in DIUR-005 included efficacy of Efmody with regards to the effect on A4, daily glucocorticoid dose, safety (specifically stress dosing and adrenal crises), impact of Efmody on body composition, bone and laboratory markers of special interest and assessment of quality of life (QoL) (Table 7). *Post-hoc* analyses included percentage of patients with good disease control, areas under the curve (AUC) of 17-OHP and A4, and 17-OHP variability expressed as the ratio of arithmetic range of concentrations over 24-hours at 24 weeks to baseline.

Table 7: DIUR-005 – study endpoints

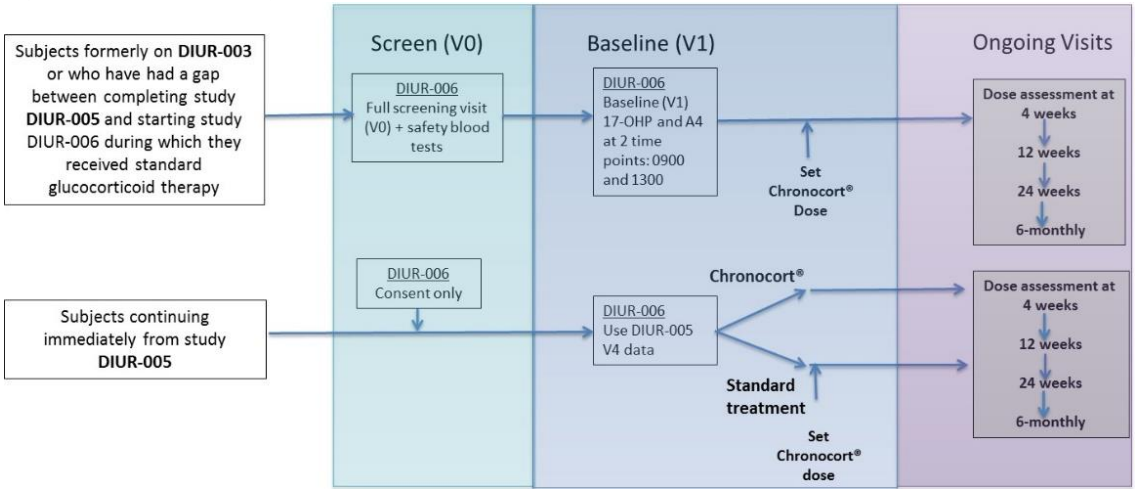
Objective	Endpoint(s)
Primary	
To demonstrate the superior efficacy of Efmody compared with standard glucocorticoid replacement therapy in the treatment of CAH based on 17-OHP	• The primary efficacy measure (PEM) was the change from baseline to 24 weeks of the mean of the 24-hour SDS profile for 17-OHP. The SDS profile was calculated as the SDS of log-transformed 17-OHP concentration unsigned.
Secondary	
To assess the safety and tolerability of Efmody treatment in adult patients with CAH over a 6-month period.	• Routine haematology, biochemistry, physical examination, vital signs, urinalysis, ECG • Clinical AEs - particular note of use of sick day rules and Addisonian crises. Under- or over-replacement with glucocorticoids were considered in the efficacy endpoints • Changes relative to standard glucocorticoid therapy in weight, BMI, waist circumference, and BP
To assess the efficacy of Efmody with regard to the effect on A4 over the 6-month treatment period.	• The 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 as a responder analysis (i.e. the number of patients achieving results in the optimal range)
To assess the impact of Efmody on body composition (using DEXA) - fat mass, lean mass and total bone density - at selected sites	• Changes relative to standard glucocorticoid therapy in body composition (DEXA) (fat mass, lean mass and total bone density) – measured at all sites except Germany
Exploratory	
Exploratory efficacy analyses: • Partial AUC of 17-OHP at 15:00–23:00, 23:00–07:00, and 07:00–15:00 • The primary endpoint measure presented for the profiles measured at 4 and 12 weeks for the purposes of titration Changes relative to standard glucocorticoid therapy in the following exploratory endpoints: • Efficacy of Efmody with regard to the effect on total testosterone levels over the 6-month treatment period • Impact of Efmody on CV risk evaluated using hsCRP • Impact of Efmody on bone markers of serum CTX and osteocalcin (after fasting) • Changes from baseline in glucose and insulin in the morning (after fasting). • Changes from baseline in HbA1c and PRA in the morning • Impact of Efmody on QoL using SF-36®, MAF and EQ-5D™ • Use of glucocorticoids at the beginning and end of the study, presented both as individual glucocorticoids used and as calculated hydrocortisone equivalents using accepted conversion constants for the calculations • Compliance in participants treated with Efmody over a 6-month period	

Objective	Endpoint(s)
Key: 17-OHP, 17-hydroxyprogesterone; A4, Androstenedione; AEs, adverse events; AUC, area under the curve; BMI, body mass index; BP, blood pressure; CAH, congenital adrenal hyperplasia; CTX, C-terminal cross-linked telopeptide; CV, cardiovascular risk; DEXA, dual energy X-ray absorptiometry; ECG, electrocardiogram; EQ-5D™, EQ-5D Standardised Health Questionnaire (5-level); HbA1c, glycated haemoglobin; hsCRP, high-sensitivity C-reactive protein; MAF, Multidimensional Assessment of Fatigue; PRA, plasma renin activity; QoL, quality of life; SDS, standard deviation score; SF-36®, Medical Outcome Short Form Health Survey Form 36. Source: Section 8.1 and 8.2 of DIUR-005 Final CSR (dated 30 Jul 2019).[28]	

DIUR-006

DIUR-006 was a Phase III, open-label extension study, designed to evaluate the safety, tolerability and efficacy of Efmody for the treatment of CAH. Patients who completed DIUR-003 or DIUR-005 were offered the opportunity to either continue Efmody therapy or to switch from their current glucocorticoid therapy to Efmody (Figure 7).

Figure 7: DIUR-006 study design



Key: 17-OHP, 17-hydroxyprogesterone; A4, Androstenedione; DEXA, Dual energy X-ray absorptiometry; V, visit.
Notes: Any patient who had a dose titration during the study will have a visit 4 weeks later. Patients with a gap between finishing DIUR-005 and starting DIUR-006 do not require an additional DEXA scan at the time they enter DIUR-006. This figure refers to Efmody as Chronocort® (as it is sourced from the DIUR-006 CSR)
Source: Figure 1. DIUR-006 CSR Interim Analysis 3 (dated 15 Dec 2020).[30]

Table 8 presents an overview of the study objectives of DIUR-006. The primary objective of DIUR-006 was to collect long-term (up to 3.7 years; study not yet final) additional safety data under monitored conditions, particularly for signs and symptoms of AI or over-treatment, use of sick days and adverse events including adrenal crises. The secondary endpoint of DIUR-006 was the assessment of long-term efficacy measured over time by assessing factors such as daily dose of hydrocortisone, disease control assessed via 17-OHP and A4, and change from pre-Efmody baseline at each visit in body composition and QoL.

Table 8: DIUR-006 – study endpoints

Objective	Endpoint(s)
Primary	
To evaluate the safety and tolerability of Efmody over time, as assessed by signs and symptoms of AI or over-treatment, use of sick day rules, adrenal crisis, AEs, laboratory measures and clinical observation.	• The primary endpoint was the safety of Efmody over time, assessed using but not limited to the following endpoints: – Signs and symptoms of AI or over-treatment – Use of sick day rules – Occurrence of adrenal crises – Occurrence of AEs – Change from pre- Efmody baseline in safety laboratory assessments at each visit – Change from pre- Efmody baseline in vital signs, weight, BMI, and waist circumference at each visit
Secondary	

Objective	Endpoint(s)
The long-term efficacy of Efmody was assessed over time by the measurement of the outcomes described in the rows below	
Total daily dose of Efmody in mg/day of hydrocortisone and by BSA during the study and the incidence of dose titrations	• Total daily dose of Efmody in mg/day of hydrocortisone and by BSA • Incidence of dose titrations
17-OHP and A4 measured at 2 time points (at 09:00 and 13:00 hours) for: • Disease control at each visit as assessed by both 17-OHP and A4 levels in the optimal and reference range, respectively, at both time points and by the proportion of dose given at night • 17-OHP and A4 SDS • Change in absolute values compared to pre-Efmody baseline values	• Disease control as assessed by both 17-OHP and A4 levels in the optimal and reference range, respectively, at 09:00 and at 13:00 and by the proportion of dose given at night • Change from pre- Efmody baseline at each visit in unsigned SDS of 17-OHP and A4 at 09:00, 13:00 and the mean of the two time points. Pre- Efmody baseline was defined as prior to the first dose of continuous Efmody i.e.: – The reassessed baseline under DIUR-006 for patients who entered from Study DIUR-003 and those patients from DIUR-005 who had a gap between completing Study DIUR-005 and starting Study DIUR-006 – Visit 4 (Week 24) from the feeder study for patients who received standard glucocorticoid replacement therapy in Study DIUR-005 and immediately entered DIUR-006 – Prior to the first Efmody dose in Study DIUR-005 for patients who received Efmody in DIUR-005 (i.e. DIUR-005 baseline visit) and immediately entered DIUR-006 – Change from pre- Efmody baseline at each visit in the absolute values of 17-OHP and A4 at 09:00 and 13:00
Changes compared to pre-Efmody baseline in: • Bone turnover markers - serum CTX and osteocalcin • Testosterone (total) • Fasting insulin and blood glucose levels, and HbA1c • HsCRP and PRA • Body composition (DEXA) (fat mass, lean mass and total bone density) (except in Germany) • QoL– SF-36®, MAF, and EQ-5D™	
Note: Pre-Efmody baseline was defined as prior to the first dose of continuous Efmody that was: • The reassessed baseline under DIUR-006 for patients who entered from Study DIUR-003 and those patients from DIUR-005 who had a gap between completing Study DIUR-005 and starting Study DIUR-006 • Visit 4 (Week 24) from the feeder study for patients who received standard glucocorticoid replacement therapy in Study DIUR-005 and immediately entered DIUR-006 • Prior to the first Efmody dose in Study DIUR-005 for patients who received Efmody in Study DIUR-005 (i.e. DIUR-005 baseline visit) and immediately entered DIUR-006	
Key: 17-OHP, 17-hydroxyprogesterone; A4, Androstenedione; AE, adverse event; AI, adrenal insufficiency; BMI, body mass index; BSA, body surface area; CTX, C-terminal cross-linked telopeptide; DEXA, dual energy X-ray absorptiometry; EQ-5D™, EQ-5D Standardised Health Questionnaire (5-level); HbA1c, glycated haemoglobin; hsCRP, high-sensitivity C-reactive protein; MAF, Multidimensional Assessment of Fatigue; PRA, plasma renin activity; QoL, quality of life; SDS, standard deviation score; SF-36®, Medical Outcome Short Form Health Survey Form 36. Source: Section 8.1 and 8.2 of DIUR-006 CSR Interim Analysis 3 (dated 15 Dec 2020).[30]	

7.1.3 Methodology and treatments administered

Following enrolment in DIUR-005, patients were admitted overnight for the assessment of 24-hour endocrine profiles for 17-OHP and A4, with blood samples 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 (Figure 6). Baseline blood samples were taken for safety assessments and to evaluate other endpoints on the second morning. Once baseline samples had been taken, patients were randomised to Efmody or to the comparator arm which was the continuation of their standard glucocorticoid therapy (either a monotherapy or combination of hydrocortisone, prednisone, prednisolone, or dexamethasone). Randomisation was stratified by baseline treatment as follows:

- Hydrocortisone only;
- Prednisone or prednisolone, alone or in combination with hydrocortisone;
- Dexamethasone, alone or in combination with any other glucocorticoid.

For patients randomised to Efmody, the starting dose was the hydrocortisone equivalent of their previous baseline glucocorticoid therapy dose. Further dose refinements/titrations were conducted in both treatment groups by blinded titrators as necessary at 4 weeks and 12 weeks after the patient had been re-admitted for further 24-hour 17-OHP and A4 profiles (Appendix B). Changes in dose of last glucocorticoid from baseline to each visit were presented as hydrocortisone equivalents using accepted conversion constants taken from Finkielstain *et al.* 2012.[8] These were: Efmody– multiply by 1; dexamethasone – multiply by 80 (up to a maximum starting dose of Efmody 30mg, split as 20mg at night and 10mg in the morning); prednisone or prednisolone – multiply by 5.
The equivalent dose of hydrocortisone received equals the product of the dose of the actual glucocorticoid replacement therapy and the conversion factor for that therapy.
The morning dose of Efmody (approximately one-third of the total daily dose) was to be taken at 07:00 hours on an empty stomach at least 1 hour before a meal and the evening dose (approximately two-thirds of the total daily dose) was to be taken at 23:00 hours at least 2 hours after the last meal of the day. The decision to make any dose adjustments (intended to optimise control of CAH according to current standard of care based on symptoms and measurement of androgens) in both treatment groups was made by two independent blinded physicians, with the actual change in dose then being made by the local Investigator looking after the patient. Dose refinements/titrations were conducted in both treatment groups at 4 weeks and 12 weeks after the patient had been re-admitted for further 24-hour 17-OHP and A4 profiles. At 6 months, all the baseline tests were repeated (including the 24-hour androgen profile). Patients could then either return to their standard glucocorticoid therapy or enter the DIUR-006 and receive Efmody on an ongoing basis. Stress doses of hydrocortisone were given for intercurrent illnesses as medically indicated according to 'sick day rules'; fludrocortisone dose adjustment was allowed if medically indicated.

DIUR-006

All patients in DIUR-005 were offered the opportunity to continue Efmody therapy or to switch from their current glucocorticoid therapy to Efmody in DIUR-006. In general, patients who completed DIUR-005 were not to have an interruption in treatment if they consented to enrol into DIUR-006; if this occurred, prior approval was to be sought from the Sponsor before the patient was entered into DIUR-006.
Following screening, all patients underwent a full set of baseline assessments before starting treatment in DIUR-006. For patients who entered from DIUR-003 and any patients from DIUR-005 who had a gap between completing DIUR-005 and starting DIUR-006 during which they received standard glucocorticoid therapy, the full set of baseline assessments were completed, including two blood samples (one at 09:00 and one at 13:00 hours) for 17-OHP and A4. A baseline dual-energy X-ray absorptiometry (DEXA) scan was only needed for patients who entered from DIUR-003. For patients who entered immediately from DIUR-005, test results from their last visit in the feeder study (Visit 4) were used for the baseline assessment, with the 09:00 and 13:00 hour results taken from the 24-hour hormone profiles conducted at the visit. Any patients who did not meet the inclusion/exclusion criteria following these blood tests were withdrawn from this study. After the baseline assessments were completed, patients were given sufficient Efmody to use until the next visit at Week 4. Patients returned to the study centre at 4, 12, and 24 weeks after starting DIUR-006, and 6-monthly thereafter for follow-up assessments (Figure 7). All patients received telephone calls at 3-monthly intervals, and unscheduled visits were arranged if necessary.
Note: A simpler version of the titration algorithm used in DIUR-005 was implemented in DIUR-006 such that it was compatible with normal care. Patients who entered immediately from DIUR-005 who were previously on Efmody continued on the same dose they had been receiving at the end of the feeder study. All other patients had their initial dose of Efmody determined using the hydrocortisone equivalent of their current treatment (immediately prior to the baseline visit). Dose titration could be performed by the investigating physician (that is the patient's own clinician rather than blinded titrators). Dose adjustments were based on clinical symptoms using the Adrenal Insufficiency Checklist and the results of the 17-OHP, and A4 levels at two time points of 09:00 and 13:00 hours. The Adrenal Insufficiency Checklist was only used to determine if symptoms of under- or over-replacement of glucocorticoids occurred over the previous 4 weeks. If there was a change of dose, an interim visit was needed in between the 6-monthly visits. Stress doses of hydrocortisone could be given for intercurrent illnesses as medically indicated

according to sick day rules. Fludrocortisone dose adjustment was made if medically indicated and was based on blood pressure measurements and laboratory data (goal supine plasma renin activity [PRA] <1.5 x ULN). If any patients had undetectable androgens at baseline on their regular medication, caution was to be taken and dose reductions performed, as necessary. Further details on patient eligibility, sample size and baseline characteristics are provided in Appendix C.

7.1.4 Efficacy and safety

7.1.4.1 Disease control: 17-OHP (DIUR-005 and DIUR-006)

Primary Endpoint Measure (PEM)

In DIUR-005, the PEM was not met, as whilst the point estimate of the treatment effect was negative in both groups (i.e. showed an improvement), and the Efmody group had a numerically greater improvement, the difference between the two treatment groups was not statistically significant (Efmody: -0.40±0.85 vs standard glucocorticoid therapy: -0.17±0.78, p=0.55;

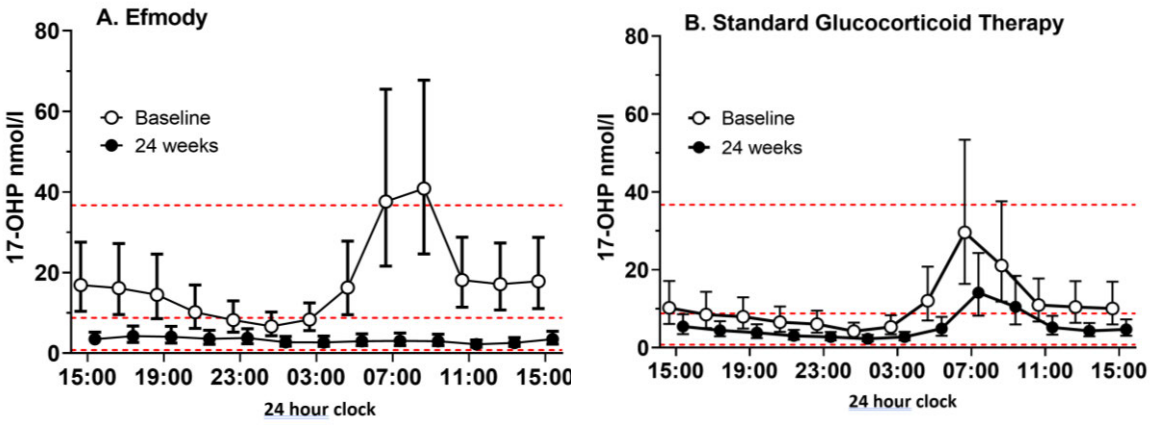
Table **9**, Figure 8 and
Figure 9). Similarly, there was no significant difference in the PEM when it was applied to prespecified subgroups. Confidence intervals and P-values are obtained from an ANCOVA (analysis of variance) model for SDS profiles- further information is presented in Table 74 in Appendix B.

The chosen PEM missed the morning improvement in biochemical control on Efmody (p=0.044) due to several factors (see Section 6 for detailed discussion). However, both the Efmody and standard glucocorticoid therapy groups achieved overall better 17-OHP control at Week 24 compared to baseline (i.e. an improvement in control of 17-OHP was observed, and by inference improved androgen profile for all patients). Notably, the change from baseline was more marked in the Efmody group, who were shown to have stable and consistent 17-OHP levels throughout the 24-hour period, as compared to the patients receiving standard glucocorticoid therapy who still had a rise in 17-OHP levels overnight and in the morning before they took their first dose of glucocorticoid (Figure 8 and
Figure **9**). Importantly, the flattened 24-hour profile of 17-OHP with Efmody was in line with that reported in healthy individuals, in whom 17-OHP displays little circadian variability within the reference range.[32, 33] Thus, the raw data analysis of the PEM demonstrates that a difference between the two groups at Week 24 was observed during the morning hours, but not throughout the day. Overall, these data indicate that the SDS profile analysis of PEM diluted the effect of the suppression of morning androgens, which was clearly seen on the graphs of the change in 24-hour profile from baseline (
Figure **9**). Thus, there was a discrepancy between the absolute raw values of the 24-hour profile of 17-OHP, which showed improved biochemical control, and the SDS profile which obscured that benefit.

While the two treatment groups of DIUR-005 were balanced, the number of patients with good baseline disease control was higher in the standard glucocorticoid therapy group compared to those randomised to Efmody (61.5% vs 37.7%. Patients in the standard glucocorticoid therapy group who were better controlled at baseline had improvement in hormonal control with glucocorticoid dose adjustments according to the protocol, but the pattern of hormone secretion did not change: the 17-OHP and A4 profiles continued to display a morning increase (

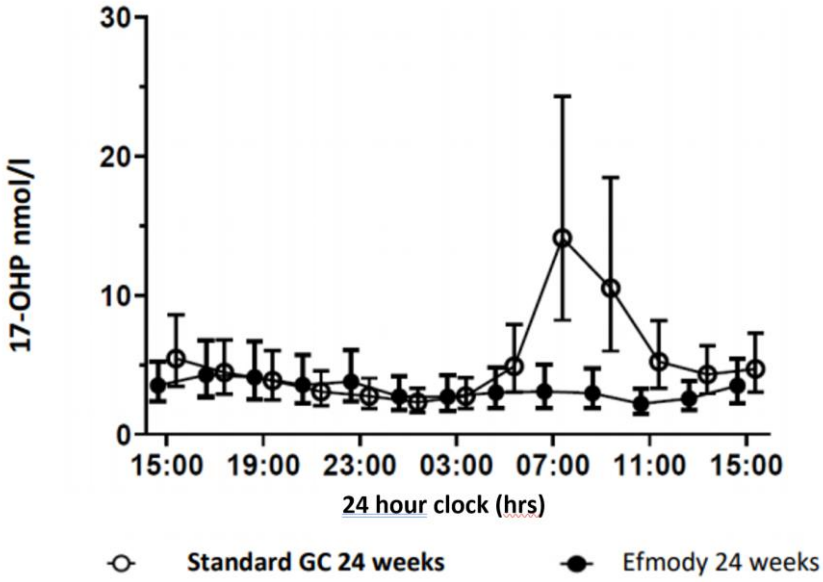
Table 9, Figure 8 and
Figure **9**). Further, control of 17-OHP, as judged by having a 17-OHP <36 nmol/l at 09:00 hours, was significantly better with Efmody than standard glucocorticoid therapy (90% vs 71%; p= 0.0048) despite the fact that, by chance, there was an unbalanced increased number of patients in control at baseline in the standard treatment arm (odds ratio of 0.379; p= 0.0157)

Figure 8: DIUR-005 – geometric mean ± 95% CI for 17-OHP (nmol/L) profile at baseline and at Week 24 by treatment group (EES)



Key: 17-OHP, 17-hydroxyprogesterone; CI, confidence interval; GC, glucocorticoid; MR-HC, modified release hydrocortisone (Efmody).
Notes: Data shown are Geometric Mean ±95% CI. The red dashed line (------) represents the limit of optimal and reference ranges for 17-OHP.
Source: DIUR-005. Figure taken from Diurnal Internal Document 2020. CH EU-EU-0066.[29]

Figure 9: Geometric mean 24-hour profile of 17-OHP after 24 weeks treatment with Efmody (closed circles) and standard therapy (open circles)



Key: 17-OHP, 17-hydroxyprogesterone; standard GC, standard glucocorticoid therapy.
Source: DIUR-005. Figure taken from Efmody Summary of Product Characteristics.[21]

Table 9: DIUR-005 – disease control with Efmody versus standard GC therapy[a]

	Efmody	Standard GC therapy	Comparison between groups
Biochemical Outcomes	**(N=53)**	**(N=52)**	**Treatment Effect[b] (95% CI), p-value[c]**
Baseline natural log 17-OHP SDS profile	1.25±0.73	1.03±0.82	
Change from baseline in natural log 17-OH SDS profile			
24-hour profile at 4 weeks	-0.37±0.63	-0.07±0.42	-0.26 (-0.46, -0.07); P=0.007
24-hour profile at 12 weeks	-0.52±0.85	-0.10±0.67	-0.30 (-0.54, -0.05); P=0.019
Primary endpoint: 24-hour profile at 24 weeks	-0.40±0.85	-0.17±0.78	-0.07 (-0.30, 0.16); P=0.55
07:00 hours –15:00 hours profile at 24 weeks	-0.69±0.96	-0.21±0.79	-0.29 (-0.56, -0.01); P=0.044

	Efmody	Standard GC therapy	Comparison between groups
Baseline natural log 17-OHP 24-hour AUC	65.2±38.5	54.0±39.2	
Change from baseline in natural log 17-OHP 24-Hour AUC			
24-hour profile at 4 weeks	-23.9±27.7	-6.1±19.3	-16.6 (-25.5, -7.8); P<0.001
24-hour profile at 12 weeks	-35.5±35.3	-13.5±28.5	-17.8 (-29.0, -6.6); P=0.002
24-hour profile at 24 weeks	-37.7±42.6	-17.8±29.0	-13.8 (-25.8, -1.8); P=0.025
Amplitude ratio of 17-OHP[d] : median (95% non-parametric CI)	0.36 (0.24, 0.65)	0.92 (0.77, 1.37)	0.38 (0.24, 0.61); P<0.001
Baseline natural log A4 24-hour AUC	21.4±30.4	13.9±32.2	
Change from baseline in natural log A4 24-hour AUC			
24-hour profile at 4 weeks	-12.5±22.2	-3.1±11.3	-8.9 (-15.6, -2.1); P=0.011
24-hour profile at 12 weeks	-20.6±23.8	-8.0±15.1	-10.9 (-18.3, -3.5); P=0.004
24-hour profile at 24 weeks	-22.9±26.9	-9.3±20.4	-10.5 (-18.7, -2.3); P=0.013

Key: 17-OHP, 17-hydroxyprogesterone; A4, Androstenedione; AUC, area under the curve; CI, confidence interval; GC, glucocorticoid; SD, standard deviation; SDS, standard deviation scores.
Notes: [a], Plus-minus values are means ± SD. CI denotes confidence interval; [b], Treatment effect is defined as least-squares mean difference (Efmody minus Standard GC) for SDS profiles and 24-hour AUC adjusted for baseline value and pre-baseline therapy; as the ratio Efmody to Standard GC for amplitude ratio; and as the odds ratio Efmody versus Standard GC for good disease control adjusted for baseline disease control status; [c], Confidence intervals and P-values are obtained from an ANCOVA (analysis of variance) model for SDS profiles and 24-hour AUC, by the Hodges-Lehmann and Wilcoxon methods respectively for amplitude ratio, and from a logistic model for good disease control; [d], Amplitude is defined as the maximum divided by the minimum over the 24-hour assessment period. The ratio is the amplitude at 24 weeks divided by the amplitude at baseline.
Source: Table adapted from Table 3 of Merke *et al.* 2021.[16]

In an exploratory analysis, the PEM was repeated using pre-specified 8-hour periods. When analysed in this way, the data demonstrated that at 24 weeks, the reduction in 17-OHP SDS was significantly greater in the Efmody group compared with the standard glucocorticoid therapy group in the morning (07:00–15:00 hours; -0.69±0.96 versus -0.21±0.79; p=0.044;

Table **9**). No other significant differences were observed in any of the other 8-hourly time periods. Thus, use of a mean score over 24 hours in the PEM obscured the impact of Efmody in the morning and early afternoon.
In a pre-specified exploratory analysis of 17-OHP control, the PEM was also analysed at 4 (prior to dose titration) and 12 weeks. At both time points, significantly better hormonal control measured using the PEM (i.e. Mean 24h 17-OHP SDS) was observed with Efmody compared with standard glucocorticoid therapy (4 weeks, -0.37±0.63 versus -0.07±0.42; p=0.007; 12 weeks, -0.52±0.85 versus -0.10±0.67, p=0.019,

Table **9**). However, by Week 24 (the PEM) after two rounds of dose titration the difference had reduced, although as mentioned above, improved hormonal control was evident in both groups at 24 weeks.
It should be noted that the titration regimen used in DIUR-005 was highly effective as evidenced by the raw data analysis of PEM which showed improved biochemical control. Along with the long-term biochemical control data from DIUR-006 (which utilised a titration scheme aligned with real-world clinical practice – see results below), these findings demonstrate that within the limits of an intensive and controlled clinical study environment, it is possible to improve control of androgens in patients with CAH significantly over that seen in current clinical practice. However, while a predefined blinded titration protocol can lead to improved hormonal control, use of such a titration requires the patient being admitted overnight and blood taken on a 2-hourly basis, which is not considered practicable or acceptable in real-world clinical practice.

Post hoc analyses: log transformed 17-OHP 24-hour AUC and 17-OHP variability

As described above, DIUR-005 failed its primary endpoint because the difference between the two groups in the morning did not translate into a difference over 24 hours at 24 weeks, i.e. Efmody was superior to standard therapy in control achieved over night and in the morning, times that are difficult to control effectively in current clinical practice; but similar in control achieved during the afternoon and evening time periods- times that are often controlled in clinical practice. The primary outcome was selected based on a Phase II trial;[20] however, the analysis was unhelpful in the Phase III randomised trial as the unsigned SDS analysis (i.e. both directions of deviations from the reference range included to account for both under-and over-treatments) overemphasised scores below the midpoint of the reference range and the logarithmic transformation and use of a mean score over 24 hours obscured the impact of Efmody in the morning and early afternoon.[16] See Section 6 for further details on issues with the PEM.

To better understand the nature of the hormonal control in the study, *post hoc* analyses were performed following regulatory agency protocol assistance. As mentioned above (with methodology described in detail in Appendix B) a post-hoc analysis of the AUC of 17-OHP over 24 hours was conducted to evaluate the impact of the use of unsigned SDS (i.e. to understand the direction of deviations from the reference range), as this can provide an estimate of overall patient exposure to 17-OHP which drives androgen-driven patient outcomes (e.g. fertility and symptomology). The analysis demonstrated a reduction in 17-OHP in both treatment groups throughout the duration of the study. However, reduction in the AUC of 17-OHP with Efmody compared with standard glucocorticoid was significantly greater at each timepoint - at 24 weeks, there was a significantly greater reduction in log transformed 17-OHP 24-hour AUC with Efmody compared with standard glucocorticoid therapy (difference in LS means: -13.8; 95% CI: [-25.8, -1.8]; p=0.025;

Table **9**) indicating that Efmody reduces exposure to 17-OHP significantly more than standard glucocorticoid therapy. A post-hoc analysis of 17-OHP variability (expressed as the ratio of arithmetic range of concentrations over 24-hours at 24 weeks to baseline) was conducted, as one of the key points raised during protocol assistance was that a 2-sided SDS (the primary endpoint measure) by its nature is not particularly sensitive to amplitude.The analysis demonstrated that at the end of the study, in the majority of patients, the 17-OHP profile was within the optimal range across 24 hours. The variability of 17-OHP over 24 hours was significantly reduced with Efmody compared with the standard glucocorticoid group. The ratio of amplitude at 24 weeks divided by amplitude at baseline was 0.36 (95% CI: 0.24, 0.65) with Efmody and 0.92 (95% CI: 0.77, 1.37) with the standard glucocorticoid regimen (p<0.001;

Table **9**). Together, the data demonstrate that Efmody reduced and normalised the amplitude (fluctuations) in the concentrations of 17-OHP and lowered the AUC for 17-OHP such that in the majority of patients the 17-OHP profile was within the reference range throughout 24 hours at the end of study.

Responder analysis

The pre-specified analysis for the number of patients classed as a responder at the 09:00 time point at Week 24 (i.e. results within the optimal range for 17-OHP) was performed using logistic regression adjusting for pre-baseline standard glucocorticoid therapy (hydrocortisone only, prednisone/prednisolone, and dexamethasone) as a covariate. The analysis demonstrated that a similar number of responders were seen in both treatment groups (30 responders in each group, Odds Ratio=[redacted]; 95% CI: [redacted]; p=[redacted]; Appendix D).

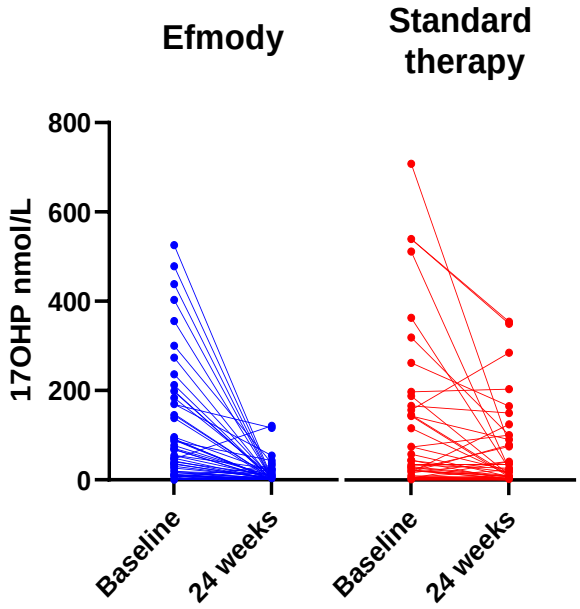
Post-hoc responder analyses for 17-OHP, which defined a responder as a patient with their 09:00 results at Week 24 in the reference range for 17-OHP (rather than the optimal range used in the pre-defined analysis.) showed similar numbers of responders at Week 24 for both groups (Efmody, n=[redacted] standard glucocorticoid therapy, n=[redacted] odds ratio=[redacted] Table 10 and Figure 10). However, at baseline, the standard glucocorticoid therapy group had a higher proportion of responders, indicating that the responder rate did not change during the study ([redacted] at both baseline and Week 24); whereas, in the Efmody group the responder rate increased from [redacted] at baseline [redacted]% at Week 24. While a subsequent analysis restricted to non-responders at baseline did not show a difference between the two treatment groups, the *post-hoc* analyses showed a higher percentage of patients in the Efmody group were responders.

Table 10: DIUR-005 – responder analysis for 09:00 hours for 17-OHP using the reference range (post-hoc analysis; EES)

Time point	Responder	Efmody([redacted], %	Standard glucocorticoid therapy (n=[redacted]), %
Baseline	Responder	[redacted]	[redacted]
	Non-responder	[redacted]	[redacted]
	Total evaluable	[redacted]	[redacted]
Visit 2 / Week 4	Responder	[redacted]	[redacted]
	Non-responder	[redacted]	[redacted]
	Total evaluable	[redacted]	[redacted]
Visit 3 / Week 12	Responder	[redacted]	[redacted]
	Non-responder	[redacted]	[redacted]
	Total evaluable	[redacted]	[redacted]
Visit 4 / Week 24	Responder	[redacted]	[redacted]
	Non-responder	[redacted]	[redacted]
	Total evaluable	[redacted]	[redacted]

Key: 17-OHP, 17-hydroxyprogesterone; EES, efficacy evaluable analysis set.
Notes: Responder status for 17-OHP is defined using the reference range of 1.2 to 6.7 nmol/L for males and 1.2 to 8.6 nmol/L for females.
Source: Secondary endpoint. Table 30. DIUR-005 Final CSR (dated 30 Jul 2019).[28]

Figure 10: DIUR-005 – individual patient changes from baseline at 09.00 hours for 17-OHP by treatment group (EES)



Key: 17-OHP, 17-hydroxyprogesterone; EES, efficacy evaluable analysis set
Source: Secondary endpoint. Figure 8. DIUR-005 Final CSR (dated 30 Jul 2019).[28]

***Post-hoc* analysis: percentage of patients with good disease control (17-OHP)**

In DIUR-005, *post hoc* analyses demonstrated that good disease control of 17-OHP at the end of the study (as judged by having a 17-OHP <36nmol/l [<1200ng/dl] at 09:00 hours), was significantly better with Efmody than with standard glucocorticoid therapy: 90.6% versus 71.2%, p=0.0018 (Table 11). This was despite there being more patients with good disease control at baseline in the standard glucocorticoid therapy arm compared with those allocated to Efmody treatment (standard glucocorticoid therapy, [redacted] Efmody, [redacted]).

Table 11: DIUR-005 – proportion of patients with good disease control* at baseline and at 24 weeks (EES)

Time point, n (%)	Efmody (N=53)	Standard GC therapy (N=52)	P-value[≠]
Baseline	[redacted]	[redacted]	-
24 weeks	48/53 (90.6)	37/52 (71.2)	**P-value** = 0.0018

Key: CI, confidence interval; EES, efficacy evaluable analysis set; GC, glucocorticoid.
Notes: *Good disease control defined as 09:00 hours 17-OHP <36 nmol/L; [#] P-values are obtained from a logistic model for good disease control.
Source: *Post-hoc* analysis. Merke *et al.* 2021[16] and Data on file.

Long term 17-OHP data from DIUR-006

In DIUR-006, a simpler, unblinded version of the titration regimen was implemented which was compatible with standard care and normal clinic times, that is 17-OHP (and A4) were measured at 09:00 and 13:00 hours, and no AUC or 24-hour SDS profiles were evaluated. This approach was more reflective of real-world style monitoring compared to DIUR-005 (where a 24-hour profile with 2-hourly blood sampling was measured; see above). Over the course of the study, clinicians who performed titration rather than blinded titrators as in DIUR-005 tended to down-titrate the patient's doses such that from Week 24 onwards, the median daily dose was [redacted] (see Section 7.1.4.3.)
In DIUR-006, over the course of the study, despite being down-titrated to a lower dose of steroid (see Section 7.1.4.3), patients achieved a similar or better disease control at each time point when compared to the percentage of patients achieving disease control at baseline (Table 12).

Table 12: DIUR-006 – patients achieving disease control at 09.00 and 13.00 hours for 17-OHP (Interim Analysis Set)

		Overall DIUR-006	DIUR-005 No Gap		DIUR-005 Gap	DIUR-003
Time point		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
09:00 17-OHP	Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13:00 17-OHP	Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: 17-OHP, 17-hydroxyprogesterone; GC, glucocorticoid.

	Overall DIUR-006	DIUR-005 No Gap		DIUR-005 Gap	DIUR-003
Time point	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes: A patient was considered a responder if their 09:00 or 13:00 results were in the optimal range for 17 OHP. For this table only, baseline is defined as the first visit (Visit 1) of Study DIUR-006 for all patients. Percentages are calculated from the total number of evaluable patients.
Data cut-off: 30 Apr 2020.
Source: Secondary endpoint. Table 15. DIUR-006 CSR Interim Analysis 3 (dated 15 Dec 2020).[30]

When disease control was evaluated by the proportion of the daily dose given at night, more responders in the overall DIUR-006 group were seen at the 09:00 hours timepoint for the highest dose proportion category (>70% to ≤90%) compared to the >50% to ≤70% category for 17-OHP. In addition, when a higher proportion of the dose was given at night-time (and so a lower proportion of the dose is taken in the morning), a higher percentage of responders were seen at the 13:00 hours timepoint for the higher night-time dose proportion categories for 17-OHP suggesting a sustained release of Efmody maintaining the androgen levels within the reference range throughout the day. Improved disease control compared to baseline was observed for 17-OHP at each timepoint and each visit up to visit 10/Month 42. The geometric means ± 95% CIs over time for 17-OHP at 09:00 and 13:00 hours are shown in Figure 11. For all the 17-OHP evaluations, the geometric mean values remained within the optimal range for the duration of the reporting period.

[redacted]

Key: 17-OHP, 17-hydroxyprogesterone; CI, confidence interval; SI, international System of Units.
Notes: Y-axis is presented on a logarithmic scale. Dotted horizontal lines denote the optimal range. Note reduced patient numbers at Months 36 and 42.
Data cut-off: 30 Apr 2020.
Source: Secondary endpoint. Figure 3. DIUR-006 CSR Interim Analysis 3 (dated 15 Dec 2020).[30]

[redacted]

Key: 17-OHP, 17-hydroxyprogesterone; CI, confidence interval; SI, international System of Units.
Notes: Y-axis is presented on a logarithmic scale. Dotted horizontal lines denote the optimal range. Note reduced patient numbers at Months 36 and 42.
Data cut-off: 30 Apr 2020.
Source: Secondary endpoint. Figure 4. DIUR-006 CSR Interim Analysis 3 (dated 15 Dec 2020).[30]

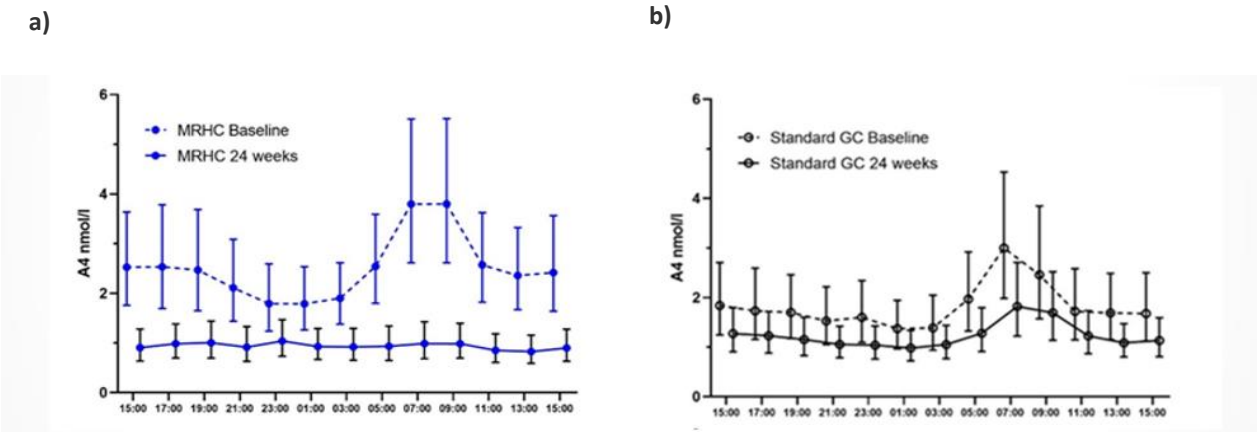
7.1.4.2 Disease control: A4

A4: change from baseline to 24 weeks in the mean of the 24-hour A4 SDS

In DIUR-005, the change from baseline to Week 24 of the PEM for A4 24-hour SDS showed little change in both treatment groups compared to baseline, and there was no difference between the two treatment groups (difference in LS means [redacted] and as expected, no significant differences between treatment groups by baseline strata were observed for A4. Evaluation of the absolute values and the changes from baseline for the primary efficacy variable for A4 by treatment group at each visit demonstrated no significant differences at any visit during the study between the two treatment groups. However, when the geometric mean A4 24-hour profiles were plotted graphically, a similar pattern was seen to 17-OHP, with patients receiving Efmody having a flatter profile showing stable and consistent A4 levels throughout the 24-hour period, while patients receiving standard

glucocorticoid therapy had a rise in A4 levels overnight and in the morning before they took their first dose of glucocorticoid (Figure 13).

Figure 13: DIUR-005 – geometric mean ± 95% CI for A4 (nmol/L) profile for Efmody (a) and (b) standard GC therapy, at baseline and at week 24 by treatment group (EES)



Key: A4, Androstenedione; CI, confidence interval; EES, efficacy evaluable analysis set; GC, glucocorticoid; MR-HC, modified release hydrocortisone (Efmody).
Source: Secondary endpoint. Figure taken from Diurnal Internal Document 2020. CH EU-EU-0066.[29] Data based on published data in Merke et al. 2021.[16]

A4 by time and responder analysis

No differences between the treatment groups were observed for any of the 8-hour profiles of A4 (exploratory analyses). When A4 was evaluated by week, there were no differences between the treatment groups at either Week 4 (difference in LS means: [redacted]) or Week 12 (difference in LS means: [redacted]). Geometric mean 24-hour profiles at Week 4 and Week 12 revealed a similar pattern to that observed at Week 24. In the pre-specified analysis, a responder was classed as having results within the reference range for A4. The data showed that the number of patients classed as a responder at the 09.00 time point at Week 24 showed no differences between the two treatment groups for A4 (p=[redacted]).

***Post hoc* analyses: log transformed A4 24-hour AUC and good disease control**

Analysis of the log-transformed AUCs for A4 demonstrated similar findings to those reported for 17-OHP. A reduction was observed in A4 AUC in both treatment groups throughout the duration of the study. At Week 24, this reduction was greater in the Efmody group compared to the standard glucocorticoid therapy (difference in LS means: -10.478; 95% CI: [-18.696, -2.259]; p=0.013; Table 13), i.e., patients were exposed to less androgen when taking Efmody. Overall, the data indicate that once 17-OHP is controlled, A4 levels fall to a nadir (as excess 17-OHP is required to generate A4 in CAH). This means that in patients where 17-OHP is controlled, A4 concentrations are not a good indicator of over-treatment. Morning (09.00 hours) good disease control for A4 was defined as below the upper limit of the normal range (A4 levels is <5.2nmol/l in males, or <7nmol/l in females [upper limits of reference range]). In DIUR-005, at baseline approximately 2/3 of patients were in control in terms of morning A4 levels. At 24 weeks, 96.2% (n=51/53) of patients were in control with Efmody (Data on File).[16]

Long term A4 data from DIUR-006

Data for A4 from the long-term DIUR-006 extension study were consistent with the findings for 17-OHP. The number of patients achieving disease control (A4 in the reference range) is shown in Table 13 at both 09:00 and 13:00 hours. Over the course of the study, similar or better disease control was seen at each time point compared to the percentage of patients achieving disease control at baseline, but this was on a lower dose of steroid. In addition, when a higher proportion of the dose was given at night-time (and so a lower proportion of the dose is taken in the morning), a higher percentage of responders were seen at the 13:00 hours timepoint for the higher night-time dose

proportion categories for A4, suggesting a sustained release of Efmody maintaining the androgen levels within the reference range throughout the day.

Table 13: DIUR-006 – patients achieving disease control at 09.00 and 13.00 hours for A4 (Interim Analysis Set)

Time point		Overall DIUR-006	DIUR-005 No Gap		DIUR-005 Gap	DIUR-003
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
09:00 A4	Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
13:00 A4	Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Month 42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: A4, androstenedione; GC, glucocorticoid.
Notes: A patient was considered a responder if their 09:00 or 13:00 results were in the reference range for A4. For this table only, baseline is defined as the first visit (Visit 1) of Study DIUR-006 for all patients. Percentages are calculated from the total number of evaluable patients.
Data cut-off: 30 Apr 2020.
Source: Secondary endpoint. Table 15. DIUR-006 CSR Interim Analysis 3 (dated 15 Dec 2020).[30]

In DIUR-006, when disease control was evaluated by the proportion of the daily dose given at night, more responders in the overall DIUR-006 group were seen at the 09:00 hours timepoint for the highest dose proportion category (>70% to ≤90%) compared to the >50% to ≤70% category for A4 (Appendix B; Table 4). When the change from pre-Efmody baseline in SDS at 09:00 and 13:00 hours for A4 was evaluated, the data indicated a worsening in hormonal control up to Week 4 at 09:00 hours and up to Month 18 at 13:00 hours. However, an increasing improvement in control compared to pre-Efmody baseline was observed thereafter (mean change of [redacted] at 09:00 hours and [redacted] at 13:00 hours at Month 30). When the mean of the SDS scores for A4 were calculated over the two time points, very little change was seen up until Month 18, however, increasing improvements were seen at Months 24 and 30. In addition, the geometric means ± 95% CIs over time for A4 at 09:00 and 13:00 hours showed that they remained around the lower limit of the reference range during this period suggesting that Efmody controls androgen excess through normalisation of 17-OHP.

7.1.4.3 Daily glucocorticoid dose

DIUR-005

The goal of CAH therapy is to effectively control excess androgen symptoms by using the lowest possible glucocorticoid dose. As mentioned above, all dose titration decisions in DIUR-005 were taken by blinded titrating physicians following a prespecified titration algorithm (that used full 24-hour hormonal profiles taken at Week 4 and Week 12 to limit the bias arising from the heterogeneous approaches to dose titration among investigators). However, the intensive blood sampling of this titration approach does not reflect clinical practice. As the androgen precursor analyses described in above demonstrated that Efmody offers better control compared with standard glucocorticoid therapy, it was important to verify the glucocorticoid doses used in each treatment arm.

In DIUR-005, one of the pre-specified endpoints was change from baseline to each visit in dose (hydrocortisone equivalent). The mean doses of glucocorticoid therapy prior to the baseline visit were similar in the two treatment groups. A *post-hoc* analysis of the median and mean dose at baseline and at Week 24 demonstrated that overall, the doses in both groups rose during the study, as a consequence of the blinded titration protocol (See Table 14). The median hydrocortisone dose equivalent was 25mg in both groups at baseline and then 30mg at Week 24 in the Efmody group compared to 31.3mg in the standard glucocorticoid therapy group. When the two dose groups were compared, there were generally more dose increases in the standard glucocorticoid therapy group (31 patients vs 28 patients) and more dose decreases in the Efmody group over the course of the study (13 patients vs 3 patients). However, it should be noted that while the median hydrocortisone dose equivalents at Week 24 are above those suggested in international guidelines, they are entirely consistent with doses in the largest published cohort studies.[8, 10]

Table 14: DIUR-005: total daily dose of steroid at baseline and week 24 (hydrocortisone dose equivalent) (SAS)

Time point	Statistics	Efmody (N=61)	Standard GC therapy (N=61)
Baseline	N	61	61
	Mean (SD)	[redacted]	[redacted]
	Median (range)	25.0 (15.0, 50.0)	25.00 (12.5, 80.0)
Visit 4/Week 24	N	58	59
	Mean (SD)	[redacted]	[redacted]
	Median (range)	30.0 (10.0, 65.0)	31.3 (12.5, 80.0)

Key: GC, glucocorticoid; SD, standard deviation; SAS, safety analysis set.
Notes: Conversion factors in converting standard GC replacement therapy to hydrocortisone are: Efmody- multiply by 1; Dexamethasone - multiply by 80; Prednisone or prednisolone - multiply by 5. The equivalent dose of hydrocortisone received equals the product of the dose of the actual GC replacement therapy and the conversion factor for that therapy.
Source: Exploratory endpoint. Table 45. DIUR-005 Final CSR (dated 30 Jul 2019);[28] Merke et al. 2021.[16]

DIUR-006

As described in Section 7.1.3 and Appendix B, the dose titration protocol in DIUR-006 more closely reflected real world patient management. This led to Efmody doses being reduced during the course of the long-term extension study. Table 15 presents the total daily dose of Efmody in DIUR-006. A reduction in the total daily dose of Efmody was seen, falling rapidly from a median total daily dose of 30mg at baseline to a median of [redacted] at Month 12 [redacted]. This dose is in line with the recommended treatment dose of 15–25mg/day for CAH in treatment guidelines. Further, over the course of the study, a reduction in the Efmody median total daily dose of 10mg was observed, which represents a clinically meaningful steroid sparing effect.[34] Similar findings were observed when the total daily dose of Efmody was evaluated by baseline body surface area (BSA).

Table 15: DIUR-006 – total daily dose of Efmody (Interim Analysis Set)

		Overall DIUR-006	DIUR-005 No Gap		DIUR-005 Gap	DIUR-003
Time interval	**Number of patients**	**Efmody (N=91), n (%)**	**Efmody (N=41), n (%)**	**Standard GC therapy (N=40), n (%)**	**Non-study GC therapy (N=6), n (%)**	**Non-study GC therapy (N=4), n (%)**
Baseline to Week 4	n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 4 to Week 12	n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 12 to Week 24	n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 24 to Month 12	n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 12 to Month 18	n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 18 to Month 24	n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 24 to Month 30	n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 30 to Month 36	n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 36 to Month 42	n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 42 to Month 48	n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

		Overall DIUR-006	DIUR-005 No Gap		DIUR-005 Gap	DIUR-003
Time interval	**Number of patients**	**Efmody (N=91), n (%)**	**Efmody (N=41), n (%)**	**Standard GC therapy (N=40), n (%)**	**Non-study GC therapy (N=6), n (%)**	**Non-study GC therapy (N=4), n (%)**

Key: GC, glucocorticoid; SD, standard deviation.
Notes: Total daily dose was summarised in mg/day of hydrocortisone where 1mg of Efmody equals 1mg of hydrocortisone. For this table only, baseline was defined as the first visit (Visit 1) of Study DIUR-006 for all patients. Participant D605/101/014 was on treatment at Visit 6, but as of data cut-off there is insufficient exposure information available to calculate the total daily dose.
Data cut-off: 30 Apr 2020.
Source: Secondary endpoint. Table 13. DIUR-006 CSR Interim Analysis 3 (dated 15 Dec 2020).[30]

7.1.4.4 Body composition

7.1.4.4.1 Bone

DIUR-005

In DIUR-005, Efmody showed no detriment in bone mineral density (BMD); no differences between the two treatment groups were seen from the DEXA scans for BMD. In addition, no differences were observed between groups in the summary statistics for the absolute values of bone markers (serum C-terminal telopeptide [CTX] and fasting osteocalcin; see DIUR-005 CSR).

DIUR-006

In DIUR-006, some small decreases were seen in BMD (total BMD measured) from pre-Efmody baseline to Month 36 [redacted] g/cm^2). However, Month 36 data should be interpreted with caution as there were only [redacted] patients with DEXA data at Month 36; of note, BMD improved up to Month 24 [redacted] where the change from baseline at Month 12 was [redacted] g/cm^2 and at Month 24 (n=39-41) it was [redacted] g/cm^2 (Appendix B; Table 6). It should be noted that when BMD changes are expressed as Z-score changes (which correct for subject age) the effect is positive being [redacted] at Month 24, and [redacted] at Month 36 (Appendix B; Table 6) particularly considering that it is a well-documented fact that bone density declines in the normal population with age. Other bone markers (serum CTX and fasting osteocalcin) remained stable over the course of the first 30 months of the study. These findings suggest a possible long-term potential.

7.1.4.4.2 Weight/fat/lean mass

DIUR-005

In DIUR-005, no differences between the two treatment groups were seen from the DEXA scans for total lean mass. For total fat mass, there was an estimated [redacted] kg least squares (LS) mean reduction in the Efmody group compared to an estimated [redacted] kg LS mean increase in the standard glucocorticoid therapy group from baseline to Week 24. However, the difference between treatment groups was not statistically significant (difference in LS means: [redacted] kg; 95% CI: [redacted] In addition, there were small increases from baseline to end of study in both the Efmody and standard glucocorticoid therapy groups in mean weight [redacted] kg, respectively) driven by increases in fat and lean mass in the standard glucocorticoid therapy group (fat mass change: 0.445 kg and lean mass change: 0.234 kg) and lean mass only in the Efmody group (fat mass change:-0.575 kg and lean mass change: 0.640 kg), but these small changes were not clinically meaningful.

DIUR-006

In DIUR-006, some small increases were seen from pre-Efmody baseline to Month 36 in the DEXA parameters for total lean mass and total fat mass (Appendix B; Table 6). However, there were only [redacted] patients with DEXA data at Month 36 which limits the conclusions that can be drawn. Total fat mass increased from pre-Efmody baseline at the start of the study and steady reduction was observed up to Month 36 (Month 12, [redacted] kg; Month 24, [redacted] kg; Month 36, [redacted] kg) reflecting dose reduction, while total lean mass increased from Month 12 to Month 36 (Month 12[redacted]). In addition, the data suggested stabilisation of weight with median change of BMI from baseline to Month 30 being [redacted] while change in weight from baseline to Month 30 [redacted] Nevertheless, the data is encouraging as it demonstrates that patients followed in the DIUR-006 study have

maintained a steady weight, despite human subjects being known to have a secular increase in weight and obesity with advancing age.[35] Weight problems are increasing in most of the European Union member states with an estimated 51.6% of the EU's adult population being overweight in 2014, with the UK, which provided significant numbers of participants to the trial, being particularly affected.[36] Adults tend to gain weight progressively approximately 0.5 to 1 kg per year.[37] In patients with CAH specifically, one study has reported that a BMI change of +1.5±2.0 kg/m^2 (mean ± SD) between baseline and 2.6 years follow-up in 15 male CAH patients while there was no change in glucocorticoid dose (glucocorticoid dose at baseline 13.8± 3.1 [mg/m^2/day] and glucocorticoid dose at 2.6 years follow-up 13.1± 3.7 [mg/m^2/day]).[38] This suggests that CAH patients treated with current glucocorticoids may be prone to gradual weight and BMI gain over time. However, long-term data from DIUR-006 suggests that the typical weight gain seen in CAH patients with current treatment (as in the general population) can be avoided with Efmody.

7.1.4.5 Laboratory assessments of special interest

DIUR-005

In DIUR-005, evaluation of laboratory assessments of special interest (hsCRP, fasting glucose, fasting insulin, homeostatic model assessment of insulin resistance [HOMA-IR], HbA1c, total testosterone, and PRA) demonstrated no major significant differences between groups. These findings were as expected given that patients had good bone and metabolic health at baseline (all but one of the patients had HbA1c within the normal range at baseline). For fasting glucose, a higher number of clinically significant high results were observed for Efmody compared to standard glucocorticoid therapy ([redacted], respectively). This is in line with the mechanism of action of Efmody which, unlike other therapies, normalises cortisol levels in the early morning with a corresponding normalising effect on morning glucose levels but no impact on HbA1c which shows that this is not causing any abnormally high glucose levels.

DIUR-006

In DIUR-006, all the laboratory assessments of special interest (total testosterone, fasting insulin, fasting glucose, HbA1c, hsCRP, and PRA) remained stable over the course of the first 30 months of the study. Again, this was expected given that patients entering DIUR-006 were within the normal range for bone and metabolic health markers (i.e. all patients entering DIUR-006 study were within the normal range of HbA1c and stayed there until the end of Interim Analysis 3). Clinically significant on-treatment results were seen for a small number of patients for testosterone, fasting glucose, hsCRP and PRA (see DIUR-006 CSR Interim Analysis 3 [dated 15 Dec 2020]).

7.1.4.6 Patient-relevant endpoints

7.1.4.6.1 Adrenal crises

DIUR-005

Of the 122 patients in DIUR-005, [redacted] had an adrenal crisis in the year before the study [redacted] of whom were randomised to receive Efmody). During the study, three (4.9%) patients in the standard glucocorticoid therapy group had an adrenal crisis (with a total [redacted] indicative adverse events [AEs]). None of the patients in the Efmody group had an adrenal crisis during DIUR-005. The AEs considered indicative of adrenal crisis in the standard glucocorticoid therapy group were: acute adrenocortical insufficiency ([redacted] patients, [redacted]%); diverticulitis, gastroenteritis viral, diarrhoea, and vomiting ([redacted] patient, [redacted]% for each AE). None of these AEs were considered causally related to standard glucocorticoid therapy.[16, 28]

DIUR-006

In DIUR-006, a total of [redacted] AEs in five patients ([redacted]%) were reported as AEs considered indicative of adrenal crisis. [redacted] patient experienced fatigue, one patient experienced adrenocortical insufficiency acute [redacted] events) and gastroenteritis viral, [redacted] patient experienced adrenocortical insufficiency acute, [redacted] patient experienced adrenocortical insufficiency acute and lower respiratory tract infection and [redacted] patient experienced vomiting [redacted] events). In the opinion of the Investigator, these AEs were not causally related to Efmody. All but [redacted] of the above events were also considered serious adverse events; the [redacted] non-serious AEs were fatigue and [redacted] events of vomiting.

A *post hoc* analysis was conducted to evaluate the number of adrenal crises per 100 patient years (up to Month 48). Out of a total of [redacted] patient years in study DIUR-006, there were [redacted] adrenal crisis events in [redacted] patients, giving an incidence rate of [redacted] events per [redacted] patient years for patients receiving Efmody (Table 16). The mean adrenal crisis

per patient was [redacted] events per [redacted] patient years, which is less than what is reported in the published literature for adult CAH patient cohorts (range: 4.9 to 10.2 adrenal crisis per 100 patient years – please see Appendix A, Table 19 for further information).

Table 16: DIUR-006 – number of adrenal crises per 100 patient years (Interim Analysis Set)

Number	Overall DIUR-006	DIUR-005 No gap		DIUR-005 Gap	DIUR-003
	Efmody (N=91)	Efmody (N=41)	Standard GC therapy (N=40)	Non-study GC therapy (N=6)	Non-study GC therapy (N=4)
Total number of patients experiencing ≥1 adrenal crisis on study, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of adrenal crises on study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patient years on study	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of adrenal crises/100 patient years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Summary statistics for total number of adrenal crises per patient / 100 patient years					
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: GC, glucocorticoid, SD, standard deviation.

Data cut-off: 30 Apr 2020.

Source: Post hoc safety analysis. Table 41. DIUR-006 CSR Interim Analysis 3 (dated 15 Dec 2020).[30]

7.1.4.7 Sick day rules

Sick day rules usage may be under-reported and under-recorded in standard clinical practice. In addition, sick day rules usage adds to the burden of CAH and also adds to the total glucocorticoid lifetime dose and associated risks. Therefore, we examined the impact of Efmody treatment on the use of sick day rules in the Efmody Phase III trials.

DIUR-005

AEs leading to use of sick day rules were reported more often in the standard glucocorticoid therapy group compared with the Efmody group (36 [69.2%] vs 26 [49.1%] patients; total of [redacted] AEs, respectively) despite similar overall rates of intercurrent illness. The most common AEs leading to use of sick day rules were fatigue (Efmody [redacted]%; standard glucocorticoid therapy, [redacted]), viral upper respiratory tract infection (Efmody, [redacted]%; standard glucocorticoid therapy, [redacted]%), and pyrexia (Efmody, [redacted]%; standard glucocorticoid therapy, [redacted]%). A difference in the overall proportion of patients with AEs leading to use of sick day rules between the Efmody and standard glucocorticoid therapy groups of >5 percentage points occurred only for pyrexia ([redacted]). AEs leading to sick day rules that were causally related to study intervention were associated with eight AEs in three patients ([redacted]) in the Efmody group, and with [redacted] AEs in two patients ([redacted]) in the standard glucocorticoid therapy group. In addition, [redacted] patients ([redacted]%) in the Efmody group and [redacted] patients ([redacted] in the standard glucocorticoid therapy group had ≥1 signs and symptoms of AI or over-treatment during the study.

DIUR-006

In total [redacted] AEs reported by [redacted] patients ([redacted]) led to use of sick day rules; a total of [redacted] AEs in five patients ([redacted]) were considered indicative of adrenal crisis. The most common AEs leading to use of sick day rules by preferred term were pyrexia ([redacted]), vomiting ([redacted]), nasopharyngitis ([redacted], fatigue ([redacted]%), and diarrhoea ([redacted]%).

7.1.4.8 Fertility

DIUR-005

As mentioned in Section 4.4, DIUR-005 enrolled non-pregnant women who were required to undergo pregnancy testing; no patients had a positive pregnancy test result at any visit. However, unexpected events considered to be of therapeutic benefit related to an improvement in reproductive hormone regulation were reported. These were as follows:

- Resumption of regular menses in five patients (Efmody, n=4; standard glucocorticoid therapy, n=1); the verbatim terms are presented in Table 17.
- Improvement in sperm characteristics for [redacted] patient receiving Efmody as measured by pre- and post intervention spermatograms (Table 17)
- Partner pregnancies of two patients in the Efmody group with full-term deliveries; one of these patients had a history of testicular adrenal rest tumour (TART) with documented sperm count improvement (<0.1 million/ml prior to Efmody and 10.3 million/ml during Efmody treatment). The two pregnancies resulted in normal deliveries.

Table 17: DIUR-005 – verbatim terms for improvement in reproductive hormone regulation by treatment group (SAS)

Category of unexpected therapeutic benefit	Verbatim terms[a]	
	Efmody (N=61)	Standard GC therapy (N=61)
Improvement in reproductive hormone regulation	[redacted]	[redacted]

Key: AEs, adverse events; GC, glucocorticoid; SAS, safety analysis set.
Notes: [a], Each line represents 1 patient.
Source: Secondary endpoint (safety). Section 12.3.1.7 of DIUR-005 Final CSR (dated 30 Jul 2019).[28]

DIUR-006

In DIUR-006, a further [redacted] patients reported an improvement in their menstrual cycle following treatment with Efmody. In addition, there were [redacted] pregnancies in the partners of patients in DIUR-006 (up to July 2021). Furthermore, [redacted] patients enrolled in DIUR-006 also became pregnant, [redacted] of which suffered an early miscarriage after transitioning to standard therapy.

7.1.4.9 Other AEs of unexpected benefit

DIUR-005

The verbatim terms for other AEs (excluding reproductive hormonal regulation) of unexpected therapeutic benefit, nearly all of which occurred in the Efmody therapy group, are presented in Table 18. In the Efmody group, patients reported improvements in mood, alertness and energy (n=[redacted]) and improvements in BMD, hair related issues and seasonal allergies (n=[redacted]). Time to onset of therapeutic benefits was variable. Improvements of mood, alertness and energy were reported between [redacted] days and [redacted] days after the start of treatment. The therapeutic benefits were sustained, and all except [redacted] of the patients continued into the extension study.

Table 18: DIUR-005 – verbatim terms for AEs of unexpected therapeutic benefit by treatment group (SAS) excluding reproductive hormonal regulation

Category of unexpected therapeutic benefit	Verbatim terms[a]	
	Efmody (N=61)	Standard GC therapy (N=61)
Improvement of mood, alertness and energy (Efmody, n=6; standard GC therapy, n=0)	[redacted]	[redacted]
Other improvements (Efmody, n=4; standard GC therapy, n=0)	[redacted]	[redacted]

Key: AEs, adverse events; GC, glucocorticoid; SAS, safety analysis set.
Notes: [a], Each line represents 1 patient.
Source: Secondary endpoint (safety). Section 12.3.1.7 of DIUR-005 Final CSR (dated 30 Jul 2019).[28]

DIUR-006

In DIUR-006, the most common AEs of therapeutic benefit outside of reproductive hormonal regulation were:

- Feeling more alert and/or less tired ([redacted] patients)
- Increased bone density [redacted] patients)
- Better quality of life [redacted] patients)
- Improvement in sleep [redacted] patients)
- Improved weight control [redacted] patients)
- Improvement in hirsutism [redacted] patients)

7.1.4.10 Change in quality of life questionnaires

DIUR-005

In DIUR-005, patient quality of life was not impaired by treatment with Efmody (Appendix B) Results of the generic QoL instruments demonstrated no major differences between the two treatment groups in any of the SF-36 parameters or in any of EQ-5D domains. Only a small change in the Global Fatigue Index (GFI) derived from the Multidimensional Assessment of Fatigue (MAF) questionnaire was observed during the study, with no differences between the two treatment groups. However, it is not surprising that there were no major differences between treatment groups given the relatively short duration of the study.

DIUR-006

Similar to DIUR-005, there were no significant differences from pre-Efmody baseline to each visit in any of the QoL measures (SF-36, MAF and EQ-5D) for the overall DIUR-006 group. While little change was seen in any of the EQ-5D domains, small numerical improvements were observed for most parameters at most time points on the SF-36. In addition, in the overall DIUR-006 group, a decrease in the Global Fatigue Index (GFI) (i.e. an improvement in feeling less fatigued) was seen over the first 18 months of the study that was maintained up to Month 30.

Further details on efficacy is provided in Appendix D.

7.1.5 Safety

DIUR-005

Overview of adverse events

In DIUR-005, the mean total treatment duration was similar in the two treatment groups (Efmody, [redacted] weeks]; standard glucocorticoid therapy[redacted] weeks] Appendix E; Table 84). The actual treatment duration was very similar to the total treatment duration in both groups, indicating very few dose interruptions. Table 19 presents an overview of the AEs observed in DIUR-005; in total there were more AEs in the Efmody group compared with the standard glucocorticoid therapy group (299 vs 224, respectively). However, more patients in the Efmody group reported AEs of unexpected therapeutic benefit (n=10, 15 events vs n=1, 1 event, respectively). This means that excluding AEs of therapeutic benefit, there were in total 284 versus 223 AEs in the Efmody and standard glucocorticoid therapy groups, respectively. Higher number of AEs in Efmody group was as expected given that comparator arm in open label study is continuation of prior therapy. In addition, fewer on-treatment serious AEs were reported for Efmody compared with standard glucocorticoid therapy ([redacted] on-treatment serious AEs in n=[redacted], respectively). None of the serious AEs were considered by the Investigators to be causally related to the drug and none had a fatal outcome. No AEs in the Efmody group were considered indicative of adrenal crisis compared with three patients (4.9%) in the standard glucocorticoid therapy group, although none of these events were considered related to the standard glucocorticoid therapy. Fewer patients in the Efmody group reported AEs leading to use of sick day rules (Efmody, n=26 [42.6%]; standard glucocorticoid therapy, n=36 [59.0%]). There were no deaths during the study.

Table 19: DIUR-005 – overview of safety (SAS)

AE category	Number of episodes/number (%) of patients[a]			
	Efmody (N=61)		Standard GC therapy (N=61)	
	Events	Patients[a]	Events	Patients[a]
Any AE	[redacted]	[redacted]	[redacted]	[redacted]
Any AE causally related to IMP	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to sick day rules	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to sick day rules causally related to IMP	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to adrenal crisis	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to adrenal crisis causally related to IMP	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to unexpected therapeutic benefit	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to unexpected therapeutic benefit causally related to IMP	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to death	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to death causally related to IMP	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Any AE leading to discontinuation causally related to IMP	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE[b]	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE causally related to IMP	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]
Any SAE leading to discontinuation causally related to IMP	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; GC, glucocorticoid; IMP, investigational medicinal product; SAE, serious adverse event; SAS, safety analysis set.
Notes: [a], Number (%) of patients with at least 1 AE; [b], number of SAE corrected from 11 to10 SAEs in the standard GC therapy group as one SAE is reported twice in same individual at the same date.

AE category	Number of episodes/number (%) of patients[a]			
	Efmody (N=61)		Standard GC therapy (N=61)	
	Events	Patients[a]	Events	Patients[a]
Includes AEs with an onset date on or after the date of first dose of randomised treatment and up to and including the last day of study treatment for participants who entered the extension study or the last day of study treatment plus 30 days for participants who did not enter the extension study. Source: Table 47. DIUR-005 Final CSR (dated 30 Jul 2019) [28]				

Most frequently reported adverse events

The majority of AEs were of the Infections and Infestations class (Efmody %; standard glucocorticoid therapy, %) and the most common AEs were headache (in both groups), viral upper respiratory tract infection (Efmody, ; standard glucocorticoid therapy,), and fatigue (Efmody, ; standard glucocorticoid therapy,). Differences between the Efmody and standard glucocorticoid therapy groups of >5 percentage points occurred for unexpected therapeutic response ( ), pyrexia ( ), nausea ( ), and increased renin ((Appendix D; Table 9).

While the majority of AEs were mild or moderate in nature, a total of patients were reported (Efmody,]; standard glucocorticoid therapy,]). Severe AEs that were reported by >1 patient were: diarrhoea (Efmody, n= ; standard glucocorticoid therapy, n=), acute adrenocortical insufficiency (Efmody, n= ; standard glucocorticoid therapy, n= and viral gastroenteritis ( ] in each group). In the Efmody group of the severe AEs were also considered serious AEs (events of appendicitis, salpingitis and adrenal insufficiency). In the standard glucocorticoid therapy group, episodes of acute adrenocortical insufficiency, diverticulitis, and viral gastroenteritis were also considered serious AEs.

Dose interruptions and study discontinuations

Possible actions taken with study intervention were dose increase, dose decrease, dose interruption, and treatment withdrawal. Dose increases were associated with a total of eight AEs (Efmody, five AEs in two participants, n= standard glucocorticoid therapy, three AEs in one participant, n= while dose decreases were associated with a total of AEs (Efmody, standard glucocorticoid therapy, The Efmody group also had an incidence of a dose interruption (n=) and a treatment withdrawal (n=) compared to in the standard group.

DIUR-006

Overview of adverse events

At the data cut-off (30 Apr 2020), the median total treatment duration was days (approximately years; Appendix D; Table 9). For patients who received Efmody in Study DIUR-005 prior to entry into DIUR-006, the overall median exposure to continuous Efmody treatment was days (i.e. over . The actual treatment duration was identical or very similar to the total treatment duration, indicating very few dose interruptions.

Table 20 presents an overview of the AEs observed in the overall DIUR-006 interim analysis Set 3. A total of of therapeutic benefit) were reported by patients AEs reported for patients ( ) were considered by the Investigators to be causally related to Efmody.) discontinued treatment due to AEs. Overall, on-treatment serious AEs were reported for of the serious AEs was considered by the Investigator to be causally related to Efmody (hypokalaemia). of the serious AEs had a fatal outcome. There were no deaths up to the end of the data period for the 30 Apr 2020 interim analysis for the DIUR-006 study.

Table 20: AEs observed in the overall DIUR-006 interim analysis Set 3

AE category	Number of events/number (%) of patients[a]									
	Overall DIUR-006		DIUR-005 No gap				DIUR-005 Gap		DIUR-003	
	Efmody (N=91)		Efmody (N=51)		Standard GC therapy (N=40)		Non-study GC therapy (N=6)		Non-study GC therapy (N=4)	
	Events	Patients[a]	Events	Patients[a]	Events	Patients[a]	Events	Patients[a]	Events	Patients[a]
Any AE	[redacted]									
Any AE causally related to Efmody	[redacted]									
Any AE leading to sick day rules	[redacted]									
Any AE leading to sick day rules causally related to Efmody	[redacted]									
Any AE leading to adrenal crisis	[redacted]									
Any AE leading to adrenal crisis causally related to Efmody	[redacted]									
Any AE leading to unexpected therapeutic benefit	[redacted]									
Any AE leading to unexpected therapeutic benefit causally related to Efmody	[redacted]									
Any AE leading to death	[redacted]									
Any AE leading to discontinuation	[redacted]									
Any AE leading to discontinuation causally related to Efmody	[redacted]									
Any SAE	[redacted]									
Any SAE causally related to Efmody	[redacted]									

AE category	Number of events/number (%) of patients[a]									
	Overall DIUR-006		DIUR-005 No gap				DIUR-005 Gap		DIUR-003	
	Efmody (N=91)		Efmody (N=51)		Standard GC therapy (N=40)		Non-study GC therapy (N=6)		Non-study GC therapy (N=4)	
	Events	Patients[a]	Events	Patients[a]	Events	Patients[a]	Events	Patients[a]	Events	Patients[a]
Any SAE leading to discontinuation	[redacted]									
Any severe AE	[redacted]									
Any AE associated with a dose increase	[redacted]									
Any AE associated with a dose increase causally related to Efmody	[redacted]									
Any AE associated with a dose decrease	[redacted]									
Any AE associated with a dose decrease causally related to Efmody	[redacted]									
Any AE associated with a dose interruption	[redacted]									

Key: AE, adverse event; GC, glucocorticoid; SAE, serious adverse event.
Notes: [a], Number (%) of patients with at least 1 AE.
Includes AEs with an onset date on or after the date of first dose of DIUR-006 Efmody (in the evening of the baseline visit) and up to and including 30 days following the end of study treatment.
Data cut-off: 30 Apr 2020.
Source: Table 28. DIUR-006 CSR Interim Analysis 3 (dated 15 Dec 2020).[30]

Most frequently reported adverse events

The most frequently reported AEs were infections and infestations ([redacted], general disorders and administration site conditions ([redacted] gastrointestinal disorders ([redacted] and nervous system disorders ([redacted] (Appendix D; Table 10). The most common AEs by preferred term were nasopharyngitis ([redacted], fatigue ([redacted], headache ([redacted], pyrexia ([redacted] and influenza ([redacted]. A total of [redacted] AEs reported [redacted]) were considered causally related to Efmody.

Adverse events by severity

Most AEs were mild or moderate; a total of [redacted] severe AEs were reported [redacted] Severe AEs that were reported by more than [redacted] patient were gastroenteritis, abdominal pain and adrenocortical insufficiency acute (each reported by [redacted] patients) and gastroenteritis viral ([redacted] patients). All other severe AEs were reported by [redacted] patient each. [redacted] patients reported multiple severe AEs. Most of the severe AEs were also serious AEs.

A total of [redacted] on-treatment serious AEs were reported by [redacted] patients ([redacted]. The most frequently reported serious AEs were infections and infestations ([redacted], gastrointestinal disorders [redacted] and endocrine disorders [redacted]. The

most common serious AEs by preferred term were adrenocortical insufficiency acute [redacted] abdominal pain, diverticulum, gastroenteritis, gastroenteritis viral, intervertebral disc protrusion, lower respiratory tract infection and pyrexia (each [redacted]%). All other serious AE preferred terms were only reported by [redacted] patient each. All except[redacted] of the on-treatment serious AEs were either moderate or severe in intensity. [redacted] serious AE was considered related to Efmody (hypokalaemia). All serious AEs except [redacted](pyrexia) were recorded as resolved.
The safety data for Efmody were in line with the well-established safety profile of hydrocortisone and do not differ significantly from that of other forms of hydrocortisone. In the Efmody clinical development programme there were no new safety concerns, and although there were slightly higher frequencies of AEs, these are consistent with the introduction of a new therapy in an open-label study. Thus, as hydrocortisone is a well-established drug with a well-characterised safety profile, it is not expected that Efmody will introduce any additional safety events over those known for hydrocortisone already. Further details on safety is provided in Appendix E.

7.1.6 Ongoing studies

The Phase III DIUR-006 extension study discussed above is ongoing and is expected to complete in the first half of 2022 (and has no further interim analyses). Completion of this trial will provide additional long-term data on the safety, tolerability and efficacy of Efmody in the treatment of CAH.

7.1.7 Comparative analyses of efficacy and safety

7.1.7.1 Method of synthesis

As described in the Section 6 it is not feasible to conduct meta-analysis due to lack of published data on currently used standard glucocorticoids. Likewise, no formal indirect or mixed treatment comparisons were conducted for Efmody as direct evidence for the clinical benefits and adverse events for Efmody compared to relevant comparators were provided in the pivotal DIUR-005 study, the largest interventional randomised controlled trial in CAH. In addition, there are no published clinical trial data for any treatments that are specifically designed to treat adolescent (aged ≥12 years) and adult CAH. Our conclusion on the lack of comparable data in the literature is supported by a Cochrane Review of glucocorticoid replacement therapy in CAH conducted by Ng *et al.* 2020 who reported a sparsity of evidence on the infeasibility of indirect or mixed treatment comparisons for current CAH glucocorticoid replacement therapies.[39] Naive indirect comparison was conducted for outcomes for which there is sufficient published data on current standard glucocorticoids that allow comparison to Efmody. Results are provided below.

7.1.7.2 Naïve indirect comparison

When the DIUR-006 data are compared with published cohort data, the naïve indirect comparison highlights that the doses of Efmody in DIUR-006, when patients were titrated under real-world conditions whilst maintaining disease control, were similar to that recommended for physiological adrenal replacement therapy and were lower doses than those reported in published cohort studies of CAH (Table 21). When gender and specific CAH type were considered, the dose reduction with Efmody compared to published cohort data on current standard of care ranges from 5–6.25mg/day, or when BSA is taken into account, 5–7.74mg/m^2/day, with a percentage dose reduction of up to 42%. Thus, disease control with Efmody has been shown to be better and also maintained at a lower dose, than that reported in the literature for standard glucocorticoid therapy. In addition, the doses of Efmody in DIUR-006 are closer to adrenal replacement doses than the usual supraphysiological dose paradigm in CAH treatment, because the glucocorticoid replacement therapy is a better approximation of physiological rhythms.

Table 21: Glucocorticoid dose in DIUR-006 compared to published cohort data

Study	Study description	Subjects and treatment	GC dose	GC dose reduction with Efmody compared to published cohort data (% GC dose reduction with Efmody)
DIUR-006	Phase III extension study of efficacy, safety and tolerability of Efmody in the treatment of CAH.	A maximum of 138 participants could be entered into this study: 16	Efmody doses* at last DIUR-006 visit: SW Female (n=53): median dose	*NA*

Study	Study description	Subjects and treatment	GC dose	GC dose reduction with Efmody compared to published cohort data (% GC dose reduction with Efmody)
	Participants who completed Study DIUR-003 or DIUR-005 were offered the opportunity either to continue Efmody therapy or to switch from their current GC therapy to Efmody	participants from DIUR-003 and 122 participants from DIUR-005. A total of 54 participants are included in this interim analysis: 27.8% male, 72.2% female, 27.8% aged 18 to <30 years, 53.7% aged ≥30 to <50 years, and 18.5% aged ≥50 to <70 years (no participants were aged ≥70 years).	[redacted]; SV Female (n=9): [redacted] All Females (n=62): [redacted] SW Male (n=24): [redacted] SV Male (n=5): [redacted] All Males (n=29): [redacted] All patients (visit 18-Month 24, n=50) median dose: [redacted]	
NIH / USA (Finkielstain et al. 2012)	Cross-sectional study of CAH included in a Natural History Study at the National Institutes of Health. National Institutes of Health (USA). (www.ClinicalTrials.gov Identifier no. NCT00250159).	244 CAH patients: 183 classic, and 61 non-classic. The cohort included 170 children (ages 0.6 to 17 yr) and 74 adults, defined as age of at least 18 yr (18 to 68 yr).	The mean GC equivalence dose in classic adult CAH patients: 17.9 ± 7.6mg/m^2 per day.	Efmody® on average 5.84mg/m^2/day lower dose equates to 33% dose reduction on Efmody®
CaHASE / UK Arlt et al. 2010**	Prospective cross-sectional study of adults with CAH attending specialised endocrine centres across the United Kingdom.	203 CAH patients (199 with 21-hydroxylase deficiency): 138 women, 65 men, median age 34 (range 18–69) years. GC treatment: Hydrocortisone (26%), prednisolone (43%), dexamethasone (19%), or a combination (10%), with reverse circadian administration in 41% of patients.	Prednisolone equivalent dose of all GCs (mg/day) day) mean (SD) and median (range): Classic male (n=62):6.1 (2.7) mg/day and 6.25 (1.67-15)mg/day; Classic females (n=101): 5.4 (1.9) mg/day and 5 (1.67-10) mg/day Corresponding HC equivalent doses (prednisone dose was multiplied by 5): Classic male: mean dose: 30.5mg/day; median dose: 31.25mg/day.	Classic CAH males: 6.25mg/day (20%); Classic CAH females: 5mg/day (20%). *(note: median dose in DIUR-006 in C-CAH male and female patients were compared to HC equivalent median dose values in CaHASE UK)*

Study	Study description	Subjects and treatment	GC dose	GC dose reduction with Efmody compared to published cohort data (% GC dose reduction with Efmody)
			Classic females: mean dose: 27mg/day; median dose: 25mg/day.	
Chakhtoura et al. 2008	Retrospective study at Necker-Enfants Malades, St-Vincent de Paul and Trousseau Hospitals, Paris, France.	38 adult patients with classical and non-classical CAH; data extracted for classic CAH patients: SW females (n=14) age: 23.5±5.5; SV females (n=5) age 27.0±5.7; all classic CAH males (n=10) age 24.2±4.5.	Median daily HC equivalent dose per m^2: SW females: 15.2 ±4.2mg/m^2/day. SV females: 20.1 ±2.9mg/m^2/day; all classic CAH males: 20.4± 4.3mg/m^2/day.	SW females: 5mg/m^2/day (33%); SV females:6.61mg/m^2/day (33%); All Classic CAH males: 7.74mg/m^2/day (38%).
Schnaider-Rezek et al. 2011	Cross sectional study	18 females with (mean ± SD, 19.3 ± 3.0 years) with 21OHD CAH. Data extracted for 11 classic CAH female patients age between 18 years and 23.3 years.	Median daily HC equivalent dose in Classic (adult) Females: 18.5mg/m^2/day	Classic CAH females: 7.71mg/m^2/day (42%).

Key: CAH, Congenital Adrenal Hyperplasia; GC, Glucocorticoid; HC, hydrocortisone; SD, Standard Deviation; SV, Simple Virilizing; SW, Salt Wasting.
Notes: *Efmody dose data is using last dose at interim analysis; hence, it is not matched for length of follow up. Salt-wasting status is derived from fludrocortisone use and is not always consistent with status recorded on medical history as several SV females were treated with Fludrocortisone, however medical history did not record SV/SW status in all subjects so Fludrocortisone status is more complete;
**Prednisolone equivalent dose data provided courtesy of the study Authors.
Source: Chakhtoura et al. 2008;[87] Arlt et al. 2010;[10] Schnaider-Rezek et al. 2011;[153] Finkielstain et al. 2012;[8] DIUR-006 post-hoc analysis - data on file.

DIUR-006 also confirmed that there were no new safety concerns with Efmody. In addition, AEs of unexpected therapeutic benefit (fatigue reduction, improvement of hirsutism, menstrual benefits) were observed with Efmody more frequently than in the standard glucocorticoid therapy group in DIUR-005; these unexpected therapeutically beneficial AEs were maintained in the long-term extension DIUR-006 study. An indirect comparison of the DIUR-006 data with published studies showed that the average frequency of adrenal crisis in DIUR-006 is lower than observed adrenal crisis frequencies per 100 treatment years in an adult USA-based (n=156)[47] and German-based (n=25)[49] CAH cohorts, 10.2 and 8.08, respectively, and similar to another German-based CAH cohort (n=122) reporting adrenal crisis frequency of 4.9 (based on patient charts) / 5.7 (based on disease-specific questionnaire)[48] (Table 22). It is worth noting that the German study with lower reported adrenal crisis frequency had a more stringent definition of crisis than in DIUR-006 whereby a patient had to be hospitalised. Identification of adrenal crises within a clinical trial setting is likely to be higher than ascertainment in retrospective studies. This indicates that the adrenal crises rates shown with Efmody compared to published cohort data in adults may actually underestimate the true benefit of Efmody in a real-world setting.

Based on published literature, frequency of adrenal crisis in children with CAH ranges from 3.4 to 10.90 crises per 100 treatment years (Odenwald et al. 2016,[53] Ishii et al. 2018,[52] Eyal et al. 2019[51]) suggesting frequency of adrenal crisis with Emfody is towards lower end of the published range in children with CAH.

Table 22: Adrenal Crisis in DIUR-006 compared to published cohort data

Study	Study description	Subjects and treatment	Adrenal crisis in adult CAH patients (crisis frequency per 100 treatment years)
Efmody: DIUR-006 (IA3)	Phase III extension study of efficacy, safety and tolerability of Efmody® in the treatment of CAH. Participants who completed Study DIUR-003 or DIUR-005 were offered the opportunity either to continue Efmody® therapy or to switch from their current GC therapy to Efmody®	A maximum of 138 participants could be entered into this study: 16 participants from DIUR-003 and 122 participants from DIUR-005	Out of a total of 221 patient years, there were [redacted] events in five patients Adrenal crises incidence rate of [redacted] patients receiving Efmody
El Maouche et al. 2018	Longitudinal assessment of CAH patients at the National Institutes of Health Clinical Center	156 patients with CAH followed at the National Institutes of Health Clinical Center over 23 years was performed. A total of 2298 visits were evaluated. Patients were followed for 9.3 ± 6.0 years. CAH cohort consisted of 81% paediatric and 19% adult patients at the first visit and 51% paediatric and 49% adult patients at the last visit. The majority (97.4%) of patients had 21-hydroxylase deficiency (62.2% SW, 26.9% SV, and 8.3% NC), and 2.6% of patients had other rare types of CAH	Crisis frequency per 100 treatment years: 10.2
Reisch et al. 2012	A cross-sectional study with detailed retrospective assessment of 122 adult 21-OHD patients (50 men, 72 women, median age 35 years, range 18-69 years)	Adrenal crisis was studied following two approaches: i) questionnaire based: 122 adult classic 21-OHD patients (50 men, 72 women, median age 35 years, range 18–69 years) completed a disease-specific questionnaire ii) patient chart based: charts of 67 classic 21-OHD patients (32 males, 35 females, median age 31 years, range 20–66 years)	Crisis frequency per 100 treatment years based on: Disease specific questionnaire data: 5.7; Patient chart data: 4.9
Zopf et al. 2017	A prospective study, patients from one German endocrine university outpatient clinic were included	The study period covered 223 patient years in which 21 adrenal crisis (AC) occurred in total (9.4 AC/100 pat years) showing a trend of more frequent ACs in PAI than in CAH patients (9.99 vs 8.08 AC/100 patient years). Forty-seven patients suffering from PAI (36 women, 11 men) and 25 patients with CAH (14 women, 11 men; salt-wasting n=17, simple-virilising n=8) were included in the study	Crisis frequency per 100 treatment years: 8.08

Key: 21-OHD; 21-hydroxylase deficiency; CAH, congenital adrenal hyperplasia; GC, glucocorticoid; IA, interim analysis; NC, PAI; SV, Simple virilising; SW, salt wasting.
Source: El-Maouche et al. 2018;[47] Reisch et al. 2012;[48] Zopf et al. 2017;[49] DIUR-006 CSR Interim Analysis 3 (dated 15 December 2020).[20]

7.2 Efficacy and safety of Efmody compared to standard glucocorticoids for adolescents (≥12 years) and adults with CAH

7.2.1 Relevant studies

Phase III DIUR-005 study provides head-to-head comparative data versus standard glucocorticoids – please see Section 7 and Appendix B and C for further information.

7.2.2 Efficacy and safety

Phase III DIUR-005 study provides head-to-head comparative data versus standard glucocorticoids – please see Section 7 and Appendix D and E for further information on efficacy and safety results, respectively.

7.2.3 Comparative analyses

As above.

8. Health economic analysis

8.1 Model

8.1.1 Summary

- The *de novo* cost-effectiveness model informing the economic analysis was developed to assess the cost-effectiveness of Efmody for the treatment of CAH in adolescents (aged ≥12 years) and adults.
- The model is structured as a series of sub-models investigating the impact of Efmody in CAH through several associated co-morbidities, and the subsequent impact on cost, health-related quality of life and mortality.
- The model aims to quantify the long-term benefit Efmody will provide from normalised cortisol and androgen levels throughout the day and night, and through the long-term reduced exposure of supraphysiological doses of steroid.
- The combined QALY impact of each of these sub-models is captured through the estimation of utility and mortality multipliers for each comorbidity.
- The comorbidities selected for inclusion are adrenal crises, obesity, fertility, height, diabetes, bone health and cardiovascular disease.
- These comorbidities were selected based on the published evidence identified in relation to each comorbidity through TLRs and interviews with seven Europe-based clinical experts to validate the importance of each comorbidity for CAH patients and whether the literature identified was appropriate to use. The TLR and clinical interviews established clear evidence for a link between androgen and cortisol levels and glucocorticoid dosing for each of the comorbidities.
- The modelling approach and the sub-models selected (adrenal crises, height, obesity and diabetes) align with those used in a previously accepted submission to the Nordic HTAs for Alkindi and the treatment of adrenal insufficiency in infants, children and adolescents (from birth to <18 years old). [18, 149]
- Efmody is the first modified-release hydrocortisone for CAH that can approximate the physiological profile of cortisol day and night. Compared with patients who received glucocorticoid replacement therapy, patients receiving Efmody had normalised androgen levels in the crucial early morning period and throughout the day. This improvement of androgen control in the morning with Efmody is aligned with its mode of action of producing a normalised 17-OHP circadian profile. To reflect this evidence, it is assumed in the model that the normalised cortisol and androgen levels resulting from Efmody would negate any impacts associated with uncontrolled androgen and cortisol levels experienced by CAH patients receiving glucocorticoid replacement therapy.
- Data from the long-term Phase III DIUR-006 extension study demonstrated sustained biochemical control with Efmody at a physiological dose (median total daily dose of 30mg at baseline, reduced to a median of 20mg in ~12 months). Glucocorticoid dose is associated with increased risk of comorbidities. Clinical experts noted that a reduction in dose of 5mg or more would be clinically meaningful and result in clinical changes for patients.[34]
- Therefore, for most sub-models, the impact of both normalising cortisol and androgen levels, and reducing glucocorticoid dose were captured in the model.
- The clinical-effectiveness data for glucocorticoid replacement therapy, utility values and cost data were taken from published sources, while resource use values were elicited from clinical interviews endocrinologists.
- The base case analysis shows that over a lifetime, patients who are treated with Efmody will experience an incremental gain of 3.66 QALYs versus glucocorticoid replacement therapy.
- The base case ICER for Efmody versus glucocorticoid replacement therapy is DKK 76,276 per QALY gained. The ICER was largely insensitive to the parameters and assumptions tested in both the one-way sensitivity analysis and the scenario analysis.
- The results indicate that Efmody is a clinically and cost-effective treatment option for patients with CAH who would otherwise receive glucocorticoid replacement therapy.

8.1.2 Model structure overview

An economic SLR to identify relevant economic evaluations, costs and HRQL values for the treatment of CAH in adults and adolescent patients has been conducted to support the development of the cost-effectiveness model for Efmody. The methodology and results of this SLR are reported in Appendix A. One relevant study in CAH patients was identified

from the economic evaluations SLR; this study estimates the lifetime disease burden of adults with CAH.[17] This disease burden model identified comprised of five sub-models (adrenal crises, cardiovascular disease, obesity, fracture and fertility) estimating life years (LYs) and QALYs for adults with CAH compared with the general population.

As no cost-effectiveness modelling studies for Efmody in the relevant patient population were identified from the economic SLR, a *de novo* economic model was developed to evaluate the cost effectiveness of Efmody in adolescents (aged ≥12 years) and adults with CAH. The model includes learnings from the health burden model, and where relevant the model which was used as the basis for Alkindi reimbursement in Nordic countries (please see Appendix L for further information on Alkindi cost-effectiveness model submitted to the TLV; the DKMA did not request cost-effectiveness analysis as part of the Alkindi general reimbursement application).[17, 18, 149]

The cost-effectiveness model was constructed in Microsoft Excel®. CAH patients have an increased risk of a wide range of comorbidities[41, 56, 67], so the model structure (depicted in Figure 14) consists of sub-models that individually investigate the impact of a specific comorbidity associated with CAH. The model has the flexibility to explore the impact of any combination of comorbidities on costs, HRQL and mortality. Efmody is the first modified-release hydrocortisone for CAH that is proven to mimic the physiological profile of cortisol day and night, resulting in controlled androgen levels (Section 5.3. and Section 7.1.4.1.). The model aims to quantify the long-term benefit Efmody will provide from normalised cortisol and androgen levels throughout the day and through the long-term reduced exposure of supraphysiological doses of steroid. The QALY impact of each of these sub-models is captured through the estimation of utility and mortality multipliers for each comorbidity, which are then combined to estimate the overall impact of all the selected comorbidities. The model structure and approach aligns with the Alkindi cost-effectiveness model and the published health burden model.[18,149]

The cost-effectiveness model considers seven sub-models (Figure 14):

- Adrenal crises
- Cardiovascular disease
- Fractures
- Obesity
- Fertility
- Diabetes
- Height

These comorbidities were selected based on a number of factors. One factor was the strength of the published evidence identified in relation to each comorbidity in a structured and targeted literature review (TLR).[75, 76] Another factor was the set of interviews conducted with seven key European clinical experts (including two Swedish experts and one Norwegian expert) to validate the importance of each comorbidity for CAH patients and whether the clinical literature identified was appropriate to use.[54]

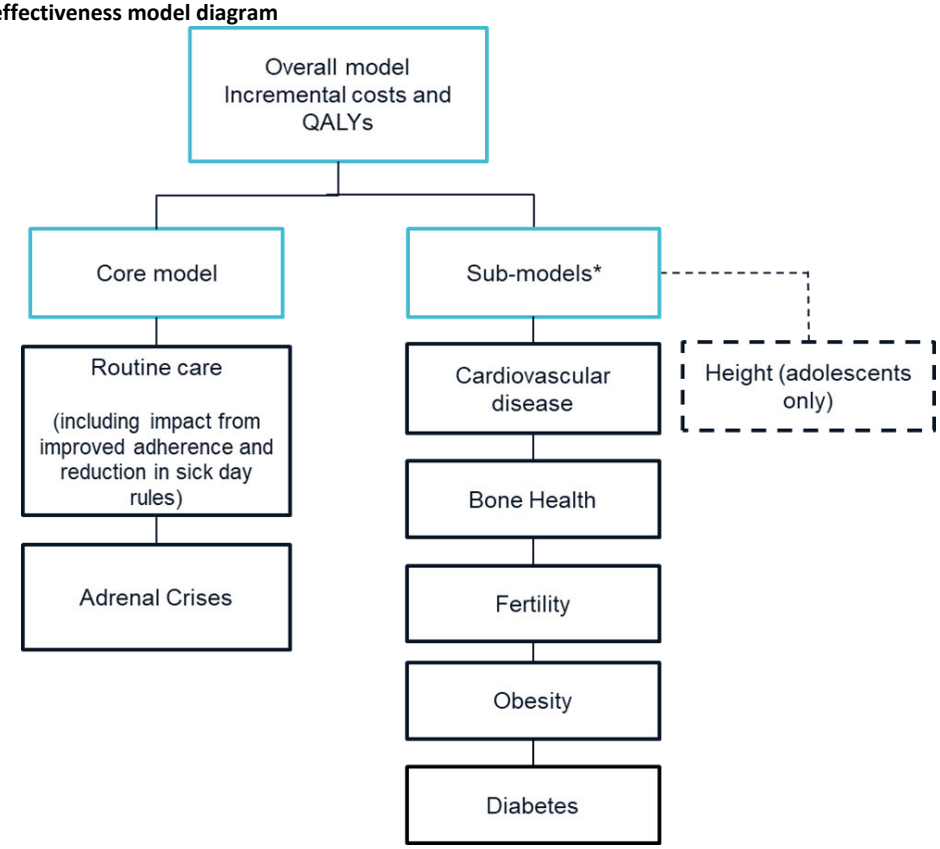
The TLR and clinical interviews established clear evidence for a link between androgen and cortisol levels and glucocorticoid dosing with each of the comorbidities. The sub-models selected align with those used in the Alkindi model (adrenal crises, height, obesity and diabetes) and the published health burden model (adrenal crises, obesity, fertility, cardiovascular disease and fractures).[17, 18,149]

For each 1-month cycle within the model, the QALY and mortality multipliers for each sub-model are estimated. These values are then combined multiplicatively to estimate overall utility and mortality multipliers for CAH, which are then applied to the age-related utility values and mortality rates in that cycle. Each sub-model multiplier is derived using a similar approach, firstly calculating the proportion of patients experiencing each event of interest in each cycle. The impact of the comorbidity on HRQL and mortality relative to the age-adjusted general population values is then estimated and multiplied by the proportion of patients experiencing the event of interest in each cycle. To estimate the total impact of CAH, these values were combined multiplicatively to estimate overall utility and mortality multipliers, which are then applied to the age-related utility values and mortality rates in that cycle.

The model also estimates all costs associated with each sub-model by multiplying the proportion of patients who are experiencing the event within each cycle by the per-cycle cost associated with the comorbidity. These costs are then combined in each cycle with the cost of the treatment and scheduled medical resource use relating to CAH.

A summarized description of the Danish model adaptation is presented in Table 23.

Figure 14: Cost-effectiveness model diagram



Key: QALY, quality-adjusted life year
Notes: *User can select whether these sub-models are included in the model; within the base case, all sub-models are considered.

Table 23. Description of the cost-effectiveness model with Danish settings

Characteristics	Description
Population	Congenital Adrenal Hyperplasia (CAH) in adults and adolescents (aged ≥12 years)
Intervention	Efmody (hydrocortisone modified-release hard capsule)
Comparators	Standard glucocorticoids (cortisol replacement therapy with glucocorticoids: hydrocortisone, prednisolone and Plenadren in adults, and hydrocortisone and Alkindi in adolescents). Only monotherapies are considered.
Outcomes	Quality of Life - Normalisation of androgen and cortisol levels - Reduction of excess glucocorticoid usage - Expected impact on - Adrenal crises - Cardiovascular disease - Diabetes - Weight/obesity - Bone health/osteoporosis - Fertility - Height Reduction of healthcare resource use (HCRU) and treatment costs as a result of improved adherence, easier monitoring and reduction of sick day rule
Perspective	Third party payer[1]
Time horizon	Lifetime[2]

Year of cost	2021
[1] The Danish Medicines Agency 's general advice 2021: All relevant costs and revenues for treatment and ill health, irrespective of the payee (county council, local authority, state, patient, relation) should be considered in line with the situation in Denmark [2] Lifetime timeframe was selected since the intervention and comparators were assumed to have impact on survival	

8.1.3 Model outcomes

Health effects are calculated in the model as LYs and QALYs. Health outcomes are calculated using a baseline of general population utilities and mortality rates; these are then adjusted using the multipliers described in Section 8.4 to account for the comorbidities associated with CAH. Health effects and costs are accrued over a lifetime time horizon, concluding when all patients either reach 100 years old or have died.

8.1.4 Perspective

The model is based on the perspective of healthcare providers, i.e., only payer perspective and direct costs are included in the base case analysis.
The clinical experts have noted that that most of CAH patients are working without any major problems, but there is a slight increase in percentage on disability pension and sick leave compared to matched controls.[121]

8.1.5 Discounting

Costs and QALYs accrued over time are discounted to estimate their present value. The base case uses an annual discount rate of 3% for both costs and effects from age 35-70 and 2 % after the age of 70 years, in line with the guidelines of the Danish Medicines Council.

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

Model inputs were taken from various sources, including the DIUR-005 and DIUR-006 clinical trials and published literature.[28, 30, 75, 76] Where data were not available, assumptions were validated by clinical experts.[54] Assumptions concerning current standard of care in CAH was based on feedback provided by the Danish trialist participating as principle investigator in the Danish clinical study site for DIUR-005 and data on glucocorticoids used in Denmark.
The Danish cost-effectiveness model is an adaptation of the core cost-effectiveness model developed for the UK settings. According to the availability of local sources, inputs have been replaced by Danish-specific data. In one hand, the sub-model efficacy and the utility decrements were not changed from the core UK model. These are based on DIUR-005, DIUR-006 clinical trials, and the TLR.
In the other hand, the following inputs were adapted and were obtained from desk research and clinical expert interviews:

- General population characteristics: weights, heights, baseline mortality, risk and mortality of CVD, and fractures,
- General setting,
- Age-related utility in general population,
- Resource use and cost.

When several publications were retrieved as possible sources for one input, the selection of model inputs was prioritized based on the quality of the study (high quality, large sample size), the place of the study (Denmark preferred, otherwise UK).
The model inputs for model settings and patient characteristics are presented in Table 24 and Table 25.

Table 24. Model settings

Parameter	Value	Comment
Model cycle length (months)	1	

Parameter	Value	Comment
Model time horizon (years)	88	
Maximum time horizon (years)	100	
Discount rate costs and effects (LYs and QALYs)	4% in the first 35 years 3% age 35-70 2% from age 71	Guidelines Danish Medicines Agency 2021

Table 25. Patient characteristics

Parameter	Value	Comment
Treatment initiation age	12.00	As per Efmody Marketing Authorisation
Proportion of female patients	0.68	Assumption based on DIUR-005 patient population and published data on CAH patients
Female puberty starting age	10.50	Brix 2018
Male puberty starting age	11.10	Brix 2018
Female puberty finishing age	15.50	Assumption from the Bergen Growth Study 2: Starting age + 5.0 years
Male puberty finishing age	16.60	Assumption from the Bergen Growth Study 2: Starting age + 5.5 years
Age of attempted conception	30.20	Statistics Denmark, equal to average age for first time mothers -1.

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

One can assume that clinical data used in the cost-effectiveness model reflects Danish clinical practice appropriately due to the following rationale:

- One Danish clinical site was included in the pivotal Phase III trial DIUR-005.
- Published clinical data regarding current standard glucocorticoids is sparse as CAH is a rare disease and there has been no innovation in the CAH for 70 years. Hence, Efmody cost-effectiveness model approach and inputs used were validated by seven European clinical experts (including Swedish and Norwegian endocrinologists) to ensure most appropriate approach and data inputs are used.
- Feedback from the Danish clinical experts was noted in the cost-effectiveness model comparator selection.
- All of the currently used glucocorticoids fail to accurately replicate the circadian rhythm of cortisol release day and overnight, and to control androgen excess. Therefore, in the cost-effectiveness model all of currently used glucocorticoids are assumed to have same clinical efficacy versus Efmody, which is the only replacement therapy that provides physiological cortisol replacement and superior androgen control with clinically meaningful steroid dose reduction.
- Danish general population and patient data was used as inputs in the cost-effectiveness model whenever possible to ensure the cost-effectiveness model reflects Danish clinical practice correctly.

8.2.2.1 Patient population

Efmody is indicated for treatment of CAH in adolescents (aged ≥12 years) and adults. This pharmaco-economic analysis therefore presents the results for the licensed population of adult and adolescent (aged ≥12 years) patients, assuming treatment initiation at age 12.

Initiating treatment at age 12 fulfils a number of unmet needs in the treatment of adolescent patients with CAH. Clinical guidelines recommend that patients with CAH receive immediate release hydrocortisone whilst growing but no guidance exists on the appropriate dose for adolescent patients, dependent on their age and size.[11] Because currently used glucocorticoid therapies do not provide physiological replacement of cortisol, the physical development of patients with CAH is impaired.[63] This leads to adult patients with CAH being below general population height, a comorbidity which is linked to a significant impact on a patient's HRQL for the remainder of their life.[59]

Excess exposure to glucocorticoids and suboptimal treatment also puts adolescents at risk of developing adverse cardiometabolic disorders (including obesity, CVD and diabetes), fractures from poor bone health and infertility. Initiating treatment with Efmody during adolescence, providing improved control of patient's androgen and cortisol levels during puberty, provides the best opportunity for optimal growth and the height deficit observed in CAH patients to be addressed. Furthermore, initiating treatment with Efmody during adolescence is expected to also reduce metabolic morbidity, which although affects CAH patients later in their life has been shown to develop during these key years.[40] Clinician opinion noted that initiating treatment with Efmody during adolescence may also improve fertility and cardiovascular outcomes at a later age.[54]

In addition, clinicians noted that initiating treatment with Efmody during adolescence would be welcome from a clinical perspective, as it would create consistency through their patient's transition to adult services as well as through its simplified regimen, which is likely to improve adherence – a key issue in this patient population. Clinicians reported the transition from paediatric to adult care was already a disruptive time for CAH patients. Therefore, transitioning patients onto Efmody during adolescence will ensure that the transition to adult services does not have any additional disruption.

As data are only available for adult patients in the Efmody clinical trials, clinical opinion was sought to understand the impact of Efmody for adolescent patients. Although clinical trial data are not available for Efmody in adolescents, through the mode of action and physiologically based pharmacokinetic model data it is expected that Efmody will not behave differently or have different efficacy and safety in adolescents aged between 12 and 18 years compared to adults (as discussed in Section 4.3). The impact of CAH is similar between adult and adolescent patients and clinical interviews with seven clinical experts confirmed that the data identified in the literature for adult CAH patients would also be applicable for adolescent patients.[54]

However, this is likely to underestimate the benefits of initiating treatment with Efmody earlier in adolescents from age 12 years. Clinicians expect that having controlled androgen and cortisol levels in the long-term through a physiological dose of glucocorticoid, particularly when started during adolescence and continued through adulthood, could have cumulative benefits that will not be captured in this economic model.[34, 54]

Scenario analysis explores the impact on results when only the adult population is considered. This scenario assumes treatment initiation at 18 years of age, when patients would be considered adults in clinical practice.[12]

Sub-group analysis was not conducted because there were no distinct patients characteristics at the baseline, nor different Efmody treatment effects between patients that would have warranted sub-group analysis. Same patient characteristics are used in the clinical documentation and cost-effectiveness model and these can be assumed to be reflective of the Danish clinical practice as described in Section 8.2.2.

8.2.2.2 Intervention

The intervention considered in the pharmaco-economic evaluation is Efmody, as outlined in Section 5.3. Efmody is the first modified-release hydrocortisone for CAH that is proven to mimic the physiological profile of cortisol day and night, resulting in controlled androgen levels with clinically meaninful steroid dose reduction.

8.2.2.3 Comparators

In line with current Danish practice (as outlined in Section 5.2.1), the comparator considered in the economic evaluation of Efmody is the current glucocorticoid replacement therapy. This includes immediate-release hydrocortisone, prednisolone and Plenadren for adults, and Alkindi for adolescents. The comparator is considered as a basket of these glucocorticoids. Based on personal communication with the Danish Efmody trialist, also dexamethasone is used in combination with hydrocortisone in adult CAH patients (not considered in the model as only glucocorticoids used as monotherapies are considered in the cost-effectiveness model). For each glucocorticoid replacement therapy the dose that provides optimal results will vary between patients, this was evident in clinical interviews where hydrocortisone prescriptions ranged between 20mg and 60mg per day.[54,12] The doses used in the model reflect clinical guidance, which recommends 15–25mg per day of hydrocortisone divided to two or three times a day.[11]

The breakdown of current glucocorticoid therapies in Denmark as standard of care applied in the Efmody model for the base case analysis is presented in Table 26. The objective of treating CAH with glucocorticoid replacement therapies is to replace missing cortisol and ensure androgen levels are controlled day and night, whilst minimising exposure to glucocorticoids. For this purpose, the various glucocorticoid replacement therapies are expected to

provide equivalent and stable control, meaning discrepancies between the usage reflected in DIUR-005 and clinical practice would not be expected to affect model results. However, benefits arising from dose reduction with Efmody are likely to be underestimated in the model results given high proportion of patients treated with Prednisolone and that patients treated with prednisolone had a greater dose reduction in DIUR-005 and DIUR-006 compared to patients treated with hydrocortisone.

Table 26. Breakdown of glucocorticoid replacement therapies in Denmark included in the model

GC treatment	Adults		Adolescents	
	Daily Dose (mg)	Usage	Daily Dose (mg) *	Usage
Hydrocortisone	25	77%	15	85%
Plenadren	30	20%	15	0%
Prednisolone	5	3%	2.8	0%
Alkindi	NA	NA	15	15%

Key: GC, glucocorticoid.
Note: Combination glucocorticoid therapies (i.e. dexamethasone in combination with hydrocortisone) are not considered in the model. Only monotherapies are considered. That is why dexamethasone which is mainly used in a combination with hydrocortisone in Denmark is not considered in the model. *Dosing for adolescents assumed to be approx. 50% of adult dose, Alkindi daily dose is estimated based on BSA in adolescents.

The breakdown of treatments that constitute the comparator arm (Table 26) was informed by feedback from clinical experts practising in Denmark (Efmody DIUR-005 Danish triallist and previous clinical interviews) and published information on availability and use of glucocorticoids in Denmark. The treatment used, and daily dosage, differs in clinical practice for adult and adolescents.

8.2.2.4 Relative efficacy outcomes

Two TLRs were conducted to identify relevant published literature required for the cost-effectiveness model for Efmody. The first TLR identified links between biomarkers (captured in the clinical trial programme) and co-morbidities associated with CAH that are of prime concern to payers. A second TLR was conducted to review published literature to identify links between the use of glucocorticoids and long-term AEs, and co-morbidities associated with CAH, such as weight/body mass index (BMI), diabetes, bone health, height, fertility and cardiovascular disease.[75, 76]

Following completion of the TLRs, the literature identified was validated in clinical interviews with seven clinicians (from Italy, Norway, Sweden and UK). The clinical experts agreed that the clinical outcomes were relevant for inclusion in the cost-effectiveness model, and the literature presented was considered reflective of clinical practice and was therefore appropriate for use in the cost-effectiveness model.[54]

The pivotal Phase III DIUR-005, first randomised controlled trial of glucocorticoid replacement therapy for patients with CAH, demonstrated that although the trial did not meet its primary endpoint (due to issues with the chosen analysis; see Sections 4 and 6), patients who received Efmody had superior hormonal control (measured via 17-OHP and A4) during the morning and early afternoon compared to those receiving glucocorticoid replacement therapy.[16]

Data from the long-term Phase III DIUR-006 extension study demonstrated a clinically meaningful steroid sparing effect of Efmody, leading to sustained biochemical control at a physiological dose. As shown in the DIUR-006 extension study, the total daily dose of Efmody was reduced from mean [redacted] (median dose of 30mg at baseline), to a mean dose of [redacted] (median dose of 20mg) at 24 months with [redacted] of patients still participating (Section 4.5.3.), which is lower than daily dose of currently used standard glucocorticoids (approx. 30mg).[8, 10, 12] The 24-hour physiological cortisol replacement that Efmody provides is important as patients benefit from normalised cortisol levels, which in turn normalise androgen levels throughout the day, and particularly in the early morning, when androgen accumulation is at its highest. Reflecting this evidence, the outcomes in the model assume that the physiological cortisol replacement, and resulting normalisation of androgen, provided by Efmody would negate the impact associated with excessive androgen and unphysiological cortisol levels experienced by CAH patients receiving glucocorticoid replacement therapy. This assumption has been validated by clinicians as part of the clinical interviews with seven clinicians and follow-up model validation interviews with leading endocrinologists.[12, 34, 54]

Efmody provides this benefit while exposing a patient to lower levels of glucocorticoids, as demonstrated in DIUR-006; here, patients showed normalised cortisol and androgen levels whilst receiving a mean dose of [redacted] of Efmody per day (median dose [redacted].[30] Comparatively, this is lower than what is used in the current clinical practice (approx. 30mg per day).[8, 10, 12] The literature identified in the TLRs reported that glucocorticoid dose is associated with increased risk of comorbidities, such as cardiovascular disease, increased weight/BMI, shorter stature, diabetes and poor bone health. Clinical experts noted that a reduction in dose of 5mg or more would be clinically meaningful and result in clinical changes for patients.[34]

Therefore, for most sub-models, the impact of both normalising cortisol and androgen levels, and reducing glucocorticoid dose were captured in the model. The link between uncontrolled androgen and cortisol levels or glucocorticoid dosing and comorbidities were validated in clinical interviews. Seven clinicians were interviewed initially. One did not believe they had enough clinical experience to comment on long-term outcomes such as BMI, CVD, bone health, fertility and diabetes. A second expert only treated adolescents and therefore did not feel comfortable discussing outcomes related to cardiovascular health which would not be seen in their cohort.

8.2.2.4.1 Adrenal crises

Patients who have CAH are at risk of experiencing an adrenal crisis, a medical emergency resulting from a lack of cortisol. This is often caused when patients become seriously ill or when patients do not take glucocorticoid replacement therapy as prescribed. An adrenal crisis is associated with numerous symptoms including vomiting, severe fatigue, fever, hypotension, hypoglycaemia, dizziness and pain in the abdomen and back.[77] Therefore, an adrenal crisis negatively impacts a patient's HRQL and usually results in hospitalisation. In some cases an adrenal crisis can be fatal. Prevention of adrenal crises in CAH patients is one of the key elements of appropriate glucocorticoid dosing under normal and stress-related situations.[11] Efmody has a simple and easy-to-remember twice-daily treatment regimen, which resulted in compliance rates of [redacted] in the randomised DIUR-005 [redacted]n the long-term follow-up study DIUR-006.[28, 30] This is significantly higher than the compliance rate seen in current practice, a UK CAH study reported mean compliance rates of 78.3% in males and 78.5% in females receiving standard glucocorticoids.[71] Improved compliance, and therefore the provision of optimal levels of cortisol, is likely to have an impact on the risk of adrenal crises in CAH patients.

Very few adrenal crises were reported during the relatively short (6 months) DIUR-005 trial, with no Efmody patients experiencing an event and only seven events occurring in the standard glucocorticoid arm. This is likely to be related to the rigorous monitoring and titration patients experience in the clinical trial which does not reflect the care available in clinical practice.[28] Therefore, data from DIUR-006 was used to inform the Efmody arm of the model, while the standard glucocorticoid arm was informed by the literature. Using results from the DIUR-006 extension study gives a more realistic presentation of clinical practice as this trial is more representative of the real-world setting. In DIUR-006, the mean frequency of adrenal crisis was reported to be [redacted] adrenal crises per 100 patient years.[30] This was the value used in the base case for the Efmody arm of the cost-effectiveness model. Several sources reporting the frequency of adrenal crises in CAH patients receiving glucocorticoid replacement therapy were identified from targeted desk research (

Table **27**).[47-49] A study by El-Maouche et al. (2018) that included 156 patients with CAH over 23 years reports a frequency of adrenal crises of 10.2 per 100 treatment years for adult patients receiving glucocorticoid replacement therapy.[47] This study was considered the most appropriate due to the larger sample size, and the definition of an adrenal crisis was closely aligned with the definition in DIUR-006 compared with alternative studies identified (

Table **27**). This was also validated by clinical experts. In DIUR-006, an adrenal crisis was defined as described by Allolio (2015), as a clinical event which improved following parenteral glucocorticoid administration. However, the DIUR-006 definition also included occasions where patients experienced at least two of the following symptoms even if they did not attend hospital and self-treated[30], such events would not be considered adrenal crises in the El Maouche study:

- Hypotension
- Nausea or vomiting
- Severe fatigue
- Fever
- Somnolence

- Hyponatraemia or hyperkalaemia
- Hypoglycaemia

Therefore, although the adrenal crisis definition used in El-Maouche et al. (2018) was considered to be similar to that used in the DIUR-006, it is still likely to have underestimated incidence compared to the trial definition. Incidence rates reported in other studies were explored in sensitivity analyses.
There is a paucity of literature available on the rate of adrenal crises experienced in adolescent patients. During the clinician interviews there were mixed opinions on whether adolescents would experience more or fewer adrenal crises than adults. Although the model allows flexibility for different assumptions for adults and adolescents, the same frequency of adrenal crisis is assumed for adolescents as adults.

Table 27. Adrenal crisis rates reported in literature

Study	Study description	Adrenal crisis definition	Adrenal crisis frequency per 100 patient years
El-Maouche et al., 2018[47]	156 patients with CAH followed at the National Institute of Health Clinical Center over 23 years was performed A total of 2298 visits were evaluated. Patients were followed for 9.3 ± 6.0 years. CAH cohort consisted of 81% paediatric and 19% adult patients at the first visit and 51% paediatric and 49% adult patients at the last visit. The majority (97.4%) of patients had 21-OHD deficiency (62.2% SW, 26.9% SV, and 8.3% NC), and 2.6% of patients had other rare types of CAH.	A hospital admission where a patient required intravenous fluids and glucocorticoids, with the resolution of their symptoms following this treatment.	10.2
Zopf et al., 2017[49]	A prospective, longitudinal study over 37.7 ± 10.1 months included 47 PAI and 25 CAH patients from one endocrine university outpatient clinic.	Parenteral glucocorticoid administration	CAH patients (n=23): 8.08
Reisch et al., 2012[48]	Adrenal crisis was studied following two approaches: i) questionnaire based: 122 adult classic 21-OHD patients (50 men, 72 women, median age 35 years, range 18–69 years) completed a disease-specific questionnaire; ii) patient chart based: charts of 67 classic 21-OHD patients (32 males, 35 females, median age 31 years, range 20–66 years)	Adrenal crises not defined. Either patient reported in a questionnaire or retrospectively gathered from medical records	Disease-specific questionnaire data: 5.7; Patient chart data: 4.9

Key: 21-OHD, 21-hydroxylase; CAH, congenital adrenal hyperplasia; NC, non-classic CAH; PAI, primary adrenal insufficiency; SV, simple virilizing; SW, salt-wasting.

Mortality

In the model it is assumed that experiencing an adrenal crisis leads to an increased risk of mortality. Mortality associated with adrenal crises is under-reported in the literature and this was validated with the clinical experts consulted. Falhammar et al. reported the causes of death in patients with CAH were adrenal crisis (42%), cardiovascular (32%), cancer (16%), and suicide (10%) and that the only significant statistical different cause of death in CAH patients compared to healthy controls was adrenal crisis (P<.001).[70] Three relevant sources were identified using a targeted literature review.[76] Falhammar et al. (2014) a retrospective study analysing 545 Swedish CAH patients, reported an adrenal crisis mortality rate of 3.9%.[70] Hahner et al. (2015) prospectively followed 423 patients with AI for 2 years, reporting 6% of adrenal crises being fatal incidences.[78] Rushworth et al. (2014)[77] investigated mortality in relation to adrenal crises in hypo-adrenal Australian patients and found that 0.9% of patients whose principal diagnosis was adrenal crisis died. During the clinical interviews conducted with seven clinical experts, feedback was mixed regarding which data source was more reflective of clinical practice. Therefore, the study by Falhammar et al. (2014) was selected to provide the mortality risk associated with adrenal crises in the model base case. The value reported in the study best reflected the feedback from the clinical experts, was the middle value in the range of possible evidence and was based on the largest cohort. During further clinical validation interviews, clinicians noted that mortality associated with adrenal crises is likely to be under reported and so the survival benefit provided

through the prevention of adrenal crises with the use of Efmody should be considered conservative. The mortality risk reported in Rushworth et al. (2014) and Hahner at al. (2018) was explored in sensitivity analysis.

Inputs as used in the model

Table 28. Adrenal crisis - Efficacy parameters

Parameter	Value	Comments/ sources
Efmody - Probability of crisis:	0.004	DIUR-006
SOC - Probability of crisis	0.009	El-Maouche et al. 2018[47]
SOC for Adolescents - Probability of crisis	0.009	El-Maouche et al. 2018[47]
Adrenal crisis mortality rate	0.039	Falhammar et al. 2014[70]
Key: SOC, standard of care		

8.2.2.4.2 Cardiovascular disease

CAH patients are at greater risk of developing cardiovascular disease (CVD) later in life. [6, 7, 40-42] Evidence was identified during TLRs linking an increased risk of CVD to uncontrolled cortisol and androgen levels and to glucocorticoid dose in CAH and AI.[75, 76] Five studies reported a positive correlation between cortisol levels and CVD risk factors. Falhammar et al. (2015) reported an increase in cardiovascular events in CAH patients compared with age-matched controls (odds ratio [OR] = 2.7 [CI 1.4, 5.3]).[41] It is important to note that published data on CVD risk in CAH is based on relatively young patients and data in older CAH patients is very sparse. This is to be expected given that glucocorticoids were introduced in the 1950s and very few of the studied CAH patients have been greater than 50 years of age. Hence, assumptions used in the model may underestimate the actual risk of CVD in CAH patients.

While the majority of experts had not experienced CVD in their patients, due to their patient populations being too young and lack of published evidence in older CAH patients, all five clinicians who were comfortable discussing these longer-term cardiovascular outcomes believed there to be a link between sub-optimal cortisol and androgen levels and CVD in older patients with CAH.[54] Some of these experts noted that optimal treatment, reducing excess GC dosing is key to reducing risk factors in CVD. The model captures both the impact of normalisation of cortisol and androgen levels and the reduction of glucocorticoid dose on the risk of CVD.

Normalisation of cortisol and androgen levels

The closely mimicked physiological release of cortisol offered by Efmody is expected to provide a normalised androgen profile in CAH and subsequent improvement in patient symptomology.[20, 27] This is expected to reduce the risk of cardiovascular issues, especially if treatment with Efmody is initiated at an early age (≥12 years) when metabolic morbidity is shown to start to develop.[40]

General population, age-adjusted, cardiovascular event risks were calculated using the QRISK3, a regression equation that considers a number of factors to calculate a 10-year cardiovascular event risk. The QRISK3 equation only generates age-adjusted 10-year cardiovascular event risks for people above the age of 24 years old, so the model assumes that patients 24 or younger were subject to no risk of cardiovascular events.[79] To model the standard glucocorticoid arm in the model, the OR reported in Falhammar et al. (2015) was applied to the general population risk using the method reported by Grant et al. (2014) to derive an age-adjusted 10-year risk of a cardiovascular event.[80] This risk was then converted to a monthly risk to reflect the cycle length used in the model.

Due to the length of follow-up, and the age of patients enrolled in the trials, neither DIUR-005 nor DIUR-006 captured data specifically focussed on CVD events, which tend to develop over a longer time period and in older patients. In the model, it is assumed that by providing physiological cortisol replacement, Efmody will reduce the increased risk of cardiovascular events in patients with CAH to reflect a risk similar to that experienced by the general population. This assumption was validated by clinical experts as part of the clinical interviews.[12, 34, 54] To reflect this in the model, the cardiovascular event risk in the Efmody arm is derived by applying a relative-effectiveness ratio to the risk in the glucocorticoid replacement therapy arm. The relative risk used in the model base case is set so that Efmody patients have the same risk of cardiovascular events as those in the general population.

Impact from reduced glucocorticoid dosing

The literature identified in the TLR reported a link between the risk of cardiovascular-related events and daily dose of glucocorticoids in CAH patients.[75, 76] It was therefore assumed that reduction in glucocorticoid dosage as seen with Efmody would reduce the risk of cardiovascular-related events. The TLR identified a study by Skov et al. (2019) that reported adjusted hazard ratios (aHRs) of CVD in Addison's disease patients receiving low, intermediate or high doses of replacement hydrocortisone compared with age-matched controls (Table 29).[42] Due to the similarities between Addison's disease and CAH, it is assumed that this link is also applicable to CAH. The use of these data was validated as part of the clinical interviews with seven clinicians.[54]

As the inputs used in the model to estimate the impact on CVD from uncontrolled cortisol and androgen levels and glucocorticoid dose were taken from the available literature where patients with CAH were treated sub-optimally with currently available glucocorticoid treatment, it is not possible to disentangle the impact caused by uncontrolled hormones and that caused by the additional exposure to glucocorticoids. As it is not possible to avoid this potential double counting, extensive sensitivity analysis has been included to test the impact of the glucocorticoid dosing on the overall results. Inclusion of both the impact of uncontrolled cortisol and androgen levels, and the glucocorticoid dosing in the base case, as well as the result model outcomes, were validated by endocrinologists.[34]

The daily dose in each cycle was tracked for each arm, and the appropriate HRs were applied to the per-cycle cardiovascular event risk. The HRs reported in Skov et al. (2019) specifically related cardiovascular risk with hydrocortisone dosage, whereas the modelled comparator arm consisted of a mixture of glucocorticoid therapies (although the majority are assumed to receive hydrocortisone). [42] Therefore, it is assumed that the risk of CVD is equal between the glucocorticoid replacement therapies.

Table 29. Risk of cardiovascular disease by daily hydrocortisone dose (Skov et al., 2019)[42]

Dose band	Females		Males	
	Daily dosage (mg)	Hazard ratio	Daily dosage (mg)	Hazard ratio
Low	18.4	1.0	20.1	0.9
Moderate	28.1	1.4	30.9	1.0
Increased	37.6	1.8	42.9	1.5

Mortality

To capture cardiovascular event-related mortality, the model included incidence rates of angina, myocardial infarction (MI) and stroke incident rates along with case fatality rates of MI and stroke events reported by Falhammar et al. (2015).[41] These were used to derive a crude fatal cardiovascular event rate. This approach mirrors the one used in the CAH burden of illness model developed by Hummel et al. (2016).[17]

Inputs as used in the model

Table 30. CVD - Efficacy parameters

Parameter label	Value	Source / Comment
Efmody reduction of CAH impact (RR vs SOC)	0.38	Assumption
CAH increased risk of CVD	2.70	Falhammar et al. 2015[41]
Key: CVD, cardiovascular disease; SOC, standard of Care; RR, risk reduction		

8.2.2.4.3 Bone health

There is strong support within the literature that patients with CAH experience poorer bone health compared with non-CAH patients.[58, 61, 64-67] During the clinical interviews, all six clinicians who were happy to discuss bone health in their patients confirmed that it is an important clinical outcome for adult CAH patients.[54]

Within a cost-effectiveness model, the included outcomes should be relevant to both patients and payers; therefore, the impact of fractures was considered a more relevant outcome for the model than BMD (which was measured in the clinical trials).[28, 30] The interviewed clinicians stated that patients with CAH have a higher risk of fractures as they age compared with that of the general population.[54] The model captures both the impact of normalisation of cortisol and

androgen levels and the reduction of glucocorticoid dose on the risk of fractures, based on feedback from the clinical interviews.

To capture health effects and costs associated with bone health, osteoporotic fractures of the hip and vertebrae (which were symptomatic), along with forearm fractures were tracked in the model. General population fracture risk data were sourced, two retrospective studies analysing the link between fracture rates and corticosteroid prescriptions for UK adults reported non-vertebrae and hip fracture risks in adults, respectively, which were deemed appropriate for Nordic clinical setting by the Swedish clinical endocrinologist[82, 83, 12] The annual incidences from the literature were converted into 1-month incidences and applied in the model. It is assumed that patients under 18 years old have the same risk as those in the 18–34 category. Data specific to osteoporotic and symptomatic vertebrae fractures were not available in the literature; therefore, osteoporotic fractures were assumed to occur at the same rate as non-vertebrae fractures and symptomatic vertebrae fractures were assumed to occur at the same rate as hip fractures. This assumption was validated by clinical experts. Functions were then applied to the general population data to capture the increased risk due to uncontrolled cortisol and androgen levels and excess glucocorticoid exposure in each arm.

Normalisation of cortisol and androgen levels

Evidence identified in the TLR suggested a link between bone health and androgen or cortisol levels.[76] A prospective, observational, cohort study (El Maouche et al., 2015) reported that higher dehydroepiandrosterone sulphate (DHEAS), a bio-marker associated with adrenal hyperplasia, was significantly, positively correlated with higher BMD at the spine, radius, and whole body in adults with CAH. The study concluded that low DHEAS may be associated with weak cortical bone independent of GC exposure.[47]

This link was validated by clinicians, with the majority of experts agreeing it was reasonable to assume there is a link between cortisol and androgen levels and bone health.[54]

In DIUR-005, Efmody showed no detriment in BMD and in DIUR-006, some small decreases were seen in BMD (total BMD measured) from pre-Efmody baseline to Month 36 [redacted] Other bone markers (serum cross-linked C-telopeptide of type I collagen and fasting osteocalcin) remained stable over the course of the first 30 months of the study (Section 7.1.4).[28, 30] Therefore, it is expected that the mimicked physiological release of cortisol offered by Efmody is expected to provide a normalised androgen profile, which will then result in improved BMD and decreased risk of fractures. This assumption has been validated by clinicians.[34]

To estimate fracture risks for patients with CAH who receive glucocorticoid replacement therapy, a relative risk compared with the general population was derived from the literature. Falhammar et al. (2013) reported that over a 10-year period, the probability of a major osteoporotic fracture was 8.1 ±4.0% in males with CAH, compared with 4.9 ±3.0% in the Swedish general population (P=0.058). The probability of a hip fracture was reported to be 2.2±2.1% in males with CAH, compared with 0.8±0.7% in the Swedish general population (P=0.050). The ratio of CAH population risk to Swedish general population risk results in estimated relative risks of 1.68 and 2.77 for osteoporotic and hip fractures, respectively.[67] The relative risk of a symptomatic vertebrae fracture for a CAH patient compared with that of the general population was assumed to be equal to the hip fracture relative risk.

In the model, it is assumed that by providing physiological cortisol replacement, Efmody will reduce the risk of fracture to reflect a risk similar to that of the general population. This assumption has been validated by clinical experts as part of the clinical interviews and subsequent model validation meetings conducted.[12, 34, 54] To reflect this in the model, the fracture risk in the Efmody arm is derived by applying a relative effectiveness ratio to the glucocorticoid replacement therapy risk. In the base case, the relative risk is set so that Efmody patients do not experience any additional risk of fractures due to uncontrolled androgen and cortisol levels (reverting the Efmody arm to be the same as general population risk); alternative values are explored in scenario analysis.

Impact from reduced glucocorticoid dosing

Glucocorticoid treatment is known to reduce BMD and put patients at increased risk of fractures, with fracture risk associated with dose of glucocorticoids.[82] There is strong evidence to support the link between glucocorticoid dosing and lower BMD in adult patients with CAH.[76] Riehl et al. (2020) reported that in women, the BMD of the lumbar spine correlated negatively with HC-equivalent dose per body surface (r^2=0.695, p<0.001) and Bachelot et al. (2007) reported that the HC dose was negatively correlated with the BMD T-score at the femoral neck (r=-0.29, p=0.04), but not at the lumbar spine (r=-0.24, p=0.10) in adult patients with CAH.[66, 84] Jääskeläinen et al. (1996) and Hagenfeldt et

al. (2000) conducted small studies in patients with CAH (32 [male and female] and 13 [female] patients, respectively), and found that current and long-term mean GC doses showed significant negative correlations with BMD.[85, 86] Evidence was also found to support a link between glucocorticoid doses and bone health. Chakhtoura et al. (2008) reported multivariate linear regression and established that the average GC dose during puberty had the most deleterious impact on both lumbar and femoral T-scores (p=0.02).[87] Further to this, Lervolino et al. (2020) reported inverse correlations between femoral neck Z-score and cortisone dose during growth periods in patients with CAH.[88] The link between glucocorticoid dosing and bone health has been validated by clinicians as part of the clinical interviews. Five out of six of the experts considered excess glucocorticoid dosing to be a key factor in detriment to bone health in both adults and adolescents and one expert said it was important in adults patients only.[54] It is therefore assumed that a reduction of glucocorticoid dose, as seen with Efmody, will result in improved bone health and thus a reduction in risk of fractures.

To incorporate the increased risk due to glucocorticoid exposure, formulae derived by Hummel et al. (2016) that establish the relative risk of fracture by daily hydrocortisone-equivalent dose were implemented in the model.[17]

As previously discussed, due to the use of data from the CAH literature where patients are receiving sub-optimally dosed glucocorticoids it is not possible to disentangle the impact caused by uncontrolled hormones and that caused by the additional exposure to glucocorticoids from the literature sources available. As it is not possible to avoid this potential double counting, extensive sensitivity analysis has been included to test the impact of the glucocorticoid dosing on the overall results. Inclusion of both the impact of uncontrolled cortisol and androgen levels, and the glucocorticoid dosing in the base case, as well as the result model outcomes, were validated by endocrinologists.[34]

Table 31. Bone health sub-model – Increased of fractures due to glucocorticoid

	Coefficient		
	(mg/day)^2	mg/day	Intercept
Osteoporotic	-0.00009	0.02670	0.9968
Hip	-0.00020	0.03430	0.9201
Vertebral	0.00000	0.07020	1.0389
Source: Hummel et al. 2016[17]			

Mortality

Excess mortality related to hip fractures are captured in the model. Mortality rates related to fractures are assumed to be zero for patients younger than 59 years old. Beyond 60 years old, mortality risks per fracture for 10-year age bands were sourced from Karampampa et al. (2015).[131] The risk ranges from 0.3% case fatality at 60–69 up to 16.9% in patients over 90 years old.

Table 32. Mortality risks per hip fracture, by age

Age group	Mortality risk
<50	0%
50–59	0%
60–69	0.3%
70–79	3.6%
80–89	8.6%
>90	16.9%
Source: Karampampa et al. 2015[131], calculation based on the distribution of UK data	

Inputs as used in the model

Table 33. Bone health - Efficacy parameters

Parameter	Values	Source/Comment
Efmody reduction of CAH impact (RR vs SOC) - Osteoporotic	0.60	Assumption
Efmody reduction of CAH impact (RR vs SOC) - Hip/Vertebrae	0.37	
Osteoporotic fracture risk: General population*	0.049	Falhammar et al. 2013[67]
Osteoporotic fracture risk: CAH*	0.08	

Hip fracture risk: General population*	0.01	
Hip fracture risk: CAH*	0.02	
Key: * 10 year probability; CAH: RR, risk ratio; SOC, Standard of Care		

8.2.2.4.4 Obesity

There is a wealth of evidence to support that patients with CAH have a higher BMI than the general population.[8, 10, 40, 41, 43-46] In the interviews with clinicians, all five clinicians who were happy to share their experience with this comorbidity agreed that greater BMI and obesity was a key issue for CAH patients (adults and adolescents). Of two clinicians who did not feel able to comment, one expert has short-term clinical experience and so did not comment on long-term outcomes such as BMI and one expert noted they do not have a high BMI patient cohort and so did not feel comfortable answering the questions. Obesity (via impact on BMI) was also included as a sub-model in the health burden model in CAH and Alkindi cost-effectiveness model. [17, 18,149]

The model captures both the impact of normalisation of cortisol and androgen levels and the reduction of glucocorticoid dose on the risk of increased BMI and obesity. To incorporate health effects associated with BMI, general population age-related data were sourced from the literature. These values were then adjusted to reflect the impact of uncontrolled hormones and glucocorticoid dosing. Adult BMI data were taken from the Scottish Health Survey 2018 (2020 revision).[90] For adolescents, BMI data could not be directly identified, instead it was derived from general population height and weight data.[135]

Normalisation of cortisol and androgen levels

As discussed in Section 7.1.4, the DIUR-006 trial demonstrates stabilisation of weight and BMI in patients receiving Efmody. [30]

The CaHASE study highlights the relationship between uncontrolled cortisol and androgen levels with increased BMI.[10] This study followed 203 CAH patients in the UK. The study reported that female CAH patients had a BMI 1.23 times that of the general population (32.9/26.7).[10] An assumption was made, and validated by clinicians, that this proportion would also be seen in the male CAH patient population. It was noted by an endocrinologist at the model validation phase that females are treated more aggressively in terms of controlling BMI as they are more sensitive to BMI change-related issues; as males are less sensitive to BMI change, a lower multiplier may be more reasonable.[12] Therefore, a scenario analysis has been included in the model which assumes a lower multiplier for males than females.

An alternative French study by Nguyen et al. (2019) was also identified; this study reported a ratio of 1.09 (25.64/23.23) between the BMI of CAH and non-CAH patients. The evidence reported by Nguyen et al. was used in scenario analyses.[92] The data from the CaHASE study are used to inform the sub-model in the base case; this is because it has a larger sample size, and during validation, clinicians noted that this was reflective of what they see in clinical practice. The multiplier from the CaHASE study was also used in the model used to support the Alkindi approval for reimbursement in Nordic countries.[18,149]

The multipliers were applied to the general population data in the model to estimate the BMI of CAH patients who received glucocorticoid replacement therapy.

In the model, it is assumed that by providing physiological cortisol replacement, Efmody will reduce BMI and the risk of obesity to reflect a risk similar to that of the general population. This assumption has been validated by clinical experts as part of the clinical interviews and subsequent model validation meetings conducted.[12, 34, 54] To incorporate this effect into the model, a relative risk is applied to the estimated BMI in the glucocorticoid replacement therapy arm. In the base case, the relative risk is assumed to be 0.81 (1/1.23), reverting the BMI of Efmody patients back to general population levels. As CAH patients would be expected to have higher BMI upon initiation of Efmody treatment, it is assumed that Efmody patients' BMI will reduce to the general population level gradually over a 12-month period; however, alternative durations are tested in scenario analyses.

Impact from reduced glucocorticoid dosing

The TLR highlighted evidence to support a link between BMI and glucocorticoid dose among patients with AI and CAH.[75, 84, 93] All five clinicians agreed that a link between glucocorticoid dosing and BMI exists and that the risk of

obesity could be reduced if clinicians were able to control their patient's CAH without the use of excess glucocorticoids.[54] This was also considered plausible by the Nordic endocrinologists.
A study identified in the TLR, Buning et al. (2017), followed 47 patients in the Netherlands with AI, exploring the effects of two different hydrocortisone doses. The study reports that BMI increased by 0.2 points in response to changing from the lower dose (15–20mg) to the higher dose (30–40mg).[93] This is reflected in the model by increasing the BMI of patients who are receiving more than 20mg per day by 0.2 units.
As previously discussed, it is not possible to disentangle the impact caused by uncontrolled hormones and that caused by the additional exposure to glucocorticoids from the literature sources available. As it is not possible to avoid this risk of double counting, extensive sensitivity analysis has been included to test the impact of the glucocorticoid dosing on the overall results. Inclusion of both the impact of uncontrolled cortisol and androgen levels, and the glucocorticoid dosing in the base case, as well as the result model outcomes, were validated by endocrinologists.[12, 54]

Mortality

It is recognised that an increased BMI, especially when categorised as obese, is associated with an increased risk of mortality. This is because BMI is positively correlated with the incidence of comorbidities such as diabetes, CVD and cancer. The model contains two approaches to reflect this increased risk.
All-cause mortality HRs were reported in Bhaskaran et al. (2018) in five unit increments above and below 25kg/m^2.[94] This approach was not used in the base case, as it is believed mortality associated with diabetes and cardiovascular disease, have been captured in other sub-models, and so inclusion may have resulted in double counting.
The alternative approach evaluates cancer-related mortality in patients with high BMI, which is not currently captured within the model. Cancer is more prevalent and more fatal in people with high BMI, particularly those categorised as obese (BMI >30kg/m^2).[95] A study by Wade et al. (2018) reported a HR of 1.01 (95% CI = 1.01, 1.02) for every BMI unit above 27.4kg/m^2.[96] The HR was implemented in the model base case to reflect the cancer-related mortality risk associated with the modelled BMI for each treatment arm. During model validation, clinicians agreed that increased cancer-related mortality would be relevant to patients with a higher BMI.[12, 34]

Inputs as used in the model

Table 34. Obesity - Efficacy parameters

Parameter		Values	Comments/ sources
SOC obesity RR vs. general population		1.23	Arlt et al. 2010[10]
Efmody obesity RR vs. general population		1.00	Assumption of "No effect"
GC related BMI increase		0.20	Buning et al. 2017[93]
Mortality	BMI change point	25.00	Krishnan Bhaskaran et al. 2018[94]
	HR per 5 BMI unit below change point	0.81	
	HR per 5 BMI unit above change point	1.21	
	BMI baseline	27.40	Wade et al. 2018[96]
	HR per BMI unit	1.01	
	Age of increased risk	56.87	

Key: SOC Standard of Care; RR risk Ratio; HR hazard ratio; BMI Body Mass Index

8.2.2.4.5 Fertility

There is strong evidence from the literature that shows fertility is an issue for both female and male patients with CAH.[10, 56, 57] Further to this in the clinical interviews, all six clinicians who work with adult CAH patients confirmed that infertility is a key issue for their patients. They all agreed there are links between androgen levels and fertility.[54]
A TLR identified literature supporting a link between the control of a patient's androgen levels and fertility outcomes (e.g. infertility, increased risk of miscarriage).[76] Further to this, results of the DIUR-005 and DIUR-006 clinical trials showed improvements in fertility, including the restoration of menstrual cycles in some of the patients receiving Efmody and in DIUR-006 there were also three pregnancies in the partners of patients.[28, 30]
There was no evidence identified within the TLRs to support a relationship between glucocorticoid dosage and fertility.[75] Therefore, this sub-model focuses solely on fertility as an outcome due to normalisation of androgen levels.

The approach used to derive conception success rates and demand for assisted conception in the CAH populations is in line with the approach used in the CAH health burden model by Hummel et al.[17] The CaHASE study reported that 25% of women and 37% of men with CAH attempted to conceive. Of those seeking conception, 54% of women and 67% of men were successful. It was assumed that any patient with controlled androgen levels would be able to achieve fertility unassisted. In the CaHASE study, 12% of women and 11% of men had controlled hormone levels (achieved using glucocorticoid replacement therapy). It was assumed that the remaining 88% of women and 89% of men who wished to conceive but did not have controlled hormones would seek assisted conception. Using these figures, a derived success rate for assisted conception was calculated as 48% (42/88) and 63% (56/89) in women and men, respectively.[10] The same assisted conception success rates are used in the Efmody arm. However, in the base case analysis it is assumed that all patients receiving Efmody will have controlled androgen levels and, as a result, be able to conceive without requiring assisted conception. As with the other clinical endpoints, these assumptions were validated with clinicians. All clinicians interviewed agreed that improving the control of androgen levels would have a positive impact on fertility of their CAH patients. [12, 54]

Inputs as used in the model

Table 35. Fertility - Efficacy parameters

Parameter label	Female	Male	Comments/ sources
CAH patients seeking fertility	0.25	0.37	Arlt 2010[10]
Success of those seeking fertility	0.54	0.67	Arlt 2010[10]
SOC - CAH patients with control of hormones SOC	0.12	0.11	Arlt 2010[10]
Efmody – CAH patients with control of hormones	1.00	1.00	Assumption

8.2.2.4.6 Diabetes

Some evidence was found to support a link between patients with CAH and an increased incidence of type 2 diabetes mellitus (T2DM) compared with the general population.[6, 8-10, 40, 41] A longitudinal study of patients with CAH by Torky et al. (2021) provides evidence that patients develop cardiovascular and metabolic morbidity, including diabetes (diabetes risk factors measured: insulin resistance and fasting hyperglycaemia) at a young age associated with treatment-related and familial factors.[40] During clinical interviews, clinical opinion on the link between diabetes and uncontrolled androgen and cortisol levels or glucocorticoid exposure was sought. Three out of five clinicians in adult care supported the link, with two uncertain. All clinicians reported they could understand why there would be a link but had not seen it in practice.[54] One clinical expert stated that diabetes is under-reported in the literature because CAH patients have historically had reduced life expectancy, meaning research in an older population (when diabetes is more common) is limited.[54] Pregnant women with CAH also have significantly more gestational diabetes than non-CAH women, which is considered a risk factor for T2DM.[34] Note that costs for gestational diabetes have not been incorporated into the model which may lead to an underestimation of the effect of Efmody on reducing healthcare costs. In the Alkindi cost-effectiveness model for patients with paediatric AI, the increased long-term risk of diabetes associated with AI was captured.[18,149]

Normalisation of cortisol and androgen levels

Evidence was identified in the literature to support a link between uncontrolled cortisol and androgen levels and increased risk of diabetes in patients with CAH.[76] Both DIUR-005 and DIUR-006 clinical trials demonstrate a stabilisation of HbA1c levels in patients receiving Efmody.[30]

Falhammar et al. (2015) reported increased odds ratio of diabetes in CAH patients compared with age-matched controls (OR = 3.0 [CI 1.6, 5.8]).[41] This value is incorporated into the model using the method outlined by Grant et al. (2014) to derive the risk of diabetes in CAH patients.[80] The value is applied to UK general population diabetes incidence rates by age, reported in Holden et al. (2013)[97] to reflect the risk of diabetes for patients in the glucocorticoid replacement therapy arm. A US-based retrospective observational study conducted by Stewart et al. (2016) reported an OR of 3.85 of CAH patients developing diabetes mellitus versus controls.[9] This has been included in the model as sensitivity analysis.

Clinical experts noted that the inputs used in the model reflect what would be expected in clinical practice for patients receiving glucocorticoid replacement therapy but noted that the model is based on conservative estimates and the risk of diabetes in CAH is likely underestimated.[12, 34]

In the model, it is assumed that by providing physiological cortisol replacement, Efmody will reduce the increased risk of diabetes to reflect a risk similar to that of the general population. This assumption has been validated by clinical experts as part of the clinical interviews and validation meetings conducted.[12, 34, 54] To reflect this in the model, the diabetes risk in the Efmody arm is derived by applying a relative effectiveness ratio to the glucocorticoid replacement therapy risk. In the base case, relative risks are applied such that Efmody patients have no additional risk of diabetes due to uncontrolled androgen and cortisol levels (reverting the Efmody arm to general population risk); alternative values are explored in scenario analyses.

Impact from reduced glucocorticoid dosing

Evidence from the literature supports a link between diabetes incidence and glucocorticoid dose.[54, 75] This link was supported by clinical experts during interviews, who agreed the link exists although it is unlikely to directly affect the adolescent population.[54] HRs between daily prednisolone dose and diabetes risk reported in Wu et al. (2020) were incorporated into the model (Table 36).[98] These HRs were applied to the diabetes risk for each treatment arm. As the model tracks daily hydrocortisone dosage, which is typically prescribed in doses four times greater than prednisolone, the daily dosage thresholds reported in Wu et al.[98] were also multiplied by four to make the results consistent. This also assumes equal risk of diabetes between prednisolone and hydrocortisone.

As previously discussed, it is not possible to disentangle the impact caused by uncontrolled hormones and that caused by the additional exposure to glucocorticoids from the literature sources available. As it is not possible to avoid this likely a risk of double counting, sensitivity analysis has been included to test the impact of the glucocorticoid dosing on the overall results. Inclusion of both the impact of uncontrolled cortisol and androgen levels, and the glucocorticoid dosing in the base case, as well as the result model outcomes, were validated by endocrinologists.[12]

Table 36. Risk of diabetes associated with glucocorticoid dose (Wu et al., 2020)[98]

Daily prednisolone (mg)	Daily hydrocortisone (mg)	Hazard ratio
>0–4.9	>0–19.9	1.9
5–14.9	20.0–59.9	2.19
15–24.9	60–99.9	3.33
25+	100+	4.34

Mortality

An elevated mortality risk associated with diabetes was applied to age-adjusted general population mortality. This elevated risk was estimated as a HR of 1.8 from Seshasai et al. (2011), which used individual-participant data on 123,205 deaths among 820,900 people across 97 prospective studies to estimate the elevated risk of death among diabetes patients, while controlling for other variables.[99] While Seshasai et al. (2011) did not investigate the CAH population, this study was previously used to provide data in the Alkindi Swedish and Norwegian cost-effectiveness model.[18,149]

Inputs as used in the model

Table 37. Diabetes - Efficacy parameters

Parameter	Value	Source / Comment
Efmody reduction of CAH impact in females (RR vs SOC)	0.25	Assumption
Efmody reduction of CAH impact in males (RR vs SOC)	0.48	
Key: RR, risk ratio; SOC, standard of care		

8.2.2.4.7 Height (adolescents only)

There is strong evidence within the literature reporting that the final height of patients with CAH is significantly below the mean height of the general population. In the clinical interviews, clinicians agreed that patient height was a key issue for CAH adolescent patients.[44-46, 54, 58-63] All seven clinicians interviewed agreed that if cortisol and androgen levels were controlled, this would positively impact their adolescent patient's growth. Height deficiency was accepted in the cost-effectiveness model for the appraisal of Alkindi in paediatric AI.[18,149]

As adults are expected to have already achieved their final height, this sub-model is only relevant for patients receiving treatment from adolescence (treatment initiation at 12 years). Therefore, this sub-model is excluded in the scenario analysis assuming treatment initiation in adult patients only.
The difference between measured height and expected height (such as the general population mean height) is measured in height standard deviation scores (HSDS), which quantifies the number of standard deviations a patient is below the general population height. For reference, the Health England survey 2018 reported the standard deviation of general population height as 7.98 cm in females and 9.79 cm in males, aged 16–25 years old.[91]

Normalisation of cortisol and androgen levels

A study by Muthusamy et al. (2010) identified in the TLR provides evidence of below average final height in the CAH population. This study involved both an SLR and a meta-analysis that combined the height data from 35 different studies in CAH patients.[59] The study reports that patients were 1.38 standard deviations below general population final height (HSDs). Based on the standard deviation reported in the Health England survey 2018, this predicted female and male CAH patients are 11cm and 13.5cm below the general population, respectively.
The height of CAH patients receiving glucocorticoid replacement therapy is modelled using Health England survey 2018 data, as Swedish equivalents were not available. The Health England survey reported mean height and standard deviations, by gender, for 10 year age bands.[91] The final height of the English general population has increased with time, therefore the greatest mean height reported in the survey (the 25–34 year old population) was used to model the final height of the general population. To reflect the height deficit reported in Muthusamy et al. (2010)[59] for CAH patients compared to general population, 1.38 times the standard deviation was deducted from the mean height. This reflects the approach previously accepted for modelling the height deficit associated with paediatric AI in the appraisal of Alkindi.[18,149]
By providing physiological cortisol replacement from the age of 12 onwards, it is expected patients treated with Efmody will not experience the full height deficit seen in patients with CAH presented in Muthusamy et al. (2010) and so final height will be more similar to the general population height.[59] However, patients are expected to start receiving Efmody only at 12 years, and not for the entirety of their growth period, therefore the expected treatment effect of Efmody on the final height has been adjusted to provide model outcomes which are clinically appropriate. Pijnenburg-Kleizen reported that the mean age when patients grew was between 9.6 years and 15.9 years in females and 11.3 years and 16.6 years in males. Taking this, we have made the simple calculation that patients would not receive Efmody for 38% of their 'growing period' in females and 13% in males and adjusted the assumed treatment effect accordingly.[63]

Impact from reduced glucocorticoid dosing

The TLR identified evidence that the dosing of glucocorticoid while a patient is growing affects their final height. This was validated in clinical interviews.[54] It is therefore assumed that a reduction of glucocorticoid dose will result in a greater final height than seen in CAH patients with higher doses of glucocorticoid. Pijnenburg-Kleizen et al. (2019) reported a link between the magnitude of reduced height in CAH patients and their mean daily hydrocortisone dose during puberty. The study reports that a patient's height was reduced by 0.13 SDS/mg/day, with the daily dose taken as an average over the pubertal growth period. The mean was calculated from treatment initiation (12 years old in the base case) to the end of puberty, which was reported in Pijnenburg-Kleizen et al. (2019) as 15.9 and 16.6 years old in females and males, respectively.[63]
When this full impact was applied in the model, the model outcomes estimated a final height for CAH patients receiving glucocorticoid therapy to be much lower than reported in the literature. As previously discussed, it is not possible to disentangle the impact caused by uncontrolled hormones and additional exposure to glucocorticoids from the literature sources available. Therefore, it is likely model outcomes include some double counting of the impact of CAH on height. Although it is not possible to avoid this, due to the large discrepancy with the literature we have reduced the modelled glucocorticoid impact by 80% to ensure model outcomes for the glucocorticoid replacement therapy aligns with published literature (CAH patients are 10-15 cm shorter than the general population).[63] The modelled final height for patients on glucocorticoid replacement therapy in the model (Table 38) is reflective of height deficits reported in the literature. Pijnenburg-Kleizen (2019) reported a median height deficit of 1.63 HSDS compared to the French general population in a retrospective study following 39 CAH patients.[63]

Table 38. Height reduction disaggregated by treatment and effect contributor

Modelled effect	Height reduction (HSDS)			
	Efmody		Glucocorticoid replacement therapy	
	Females	Males	Females	Males
Uncontrolled hormones	0.53	0.18	1.38	1.38
Glucocorticoid exposure	0.26	0.25	0.27	0.25
Total	0.79	0.43	1.65	1.63
Key: HSDS, height standard deviation score.				

Inputs as used in the model

Table 39. Height - Efficacy parameters

Parameter	Value	Comments/ sources
Final height reduction due to uncontrolled hormones in CAH patients (HSDS below the general population)	1.38	Muthusamy et al. 2010[59]
Final height reduction due to glucocorticoids (HSDS reduction per mg/m^2/day)	0.026	Assumption based on Pijnenburg-Kleizen 2019 et al.[63] (80% reduction applied to GC impact)
Percentage of female patients not receiving Efmody during their pubescent period	0.38	Assumption
Percentage of male patients not receiving Efmody during their pubescent period	0.13	Assumption
Key: SDS, standard deviation score; RR, risk ratio; SOC, Standard of care.		

8.2.2.5 Adverse reaction outcomes

In clinical trials, Efmody has been shown to be well tolerated (see Section 7.1.5.), with the incidence of observed AEs consistent with the well-established experience with hydrocortisone (the active component of Efmody). For this reason, treatment-related AEs were not considered in the cost-effectiveness model.

8.3 Extrapolation of relative efficacy

Efmody effect is assumed to remain the same (no decrease / increase over time) and a lifetime horizon is applied in the model. Same clinical effects are assumed for adult and adolescent CAH patients as described in Section 8.2.2.1. Hence, extrapolation of relative efficacy beyond what is presented in the Section 8.2.2.5 has not been conducted.

8.3.1 Time to event data – summarized:

As above - not applicable to Efmody cost-effectiveness model.

8.4 Documentation of health-related quality of life (HRQoL)

The literature searches are presented in the Appendix H.

8.4.1 Overview of health state utility values (HSUV)

Patients with CAH have an increased risk of associated comorbidities.[41, 56, 67] As a result, adult and adolescent patients with CAH are expected to have a lower HRQL compared with healthy adults and adolescents. In the clinical interviews, all experts consider a large majority of their adult and adolescent patients with CAH to have a reduced HRQL compared to the general population.[54]

There was no negative impact on patient HRQL when measured using generic HRQL questionnaires with Efmody.[28]

Only the health burden model by Hummel et al. (2016) identified in the economic evaluations SLR was considered to report data on HRQL that could be utilised in the cost-effectiveness model.[17]

The TLR did not identify any literature suggesting that cortisol and androgen levels have a direct impact on a patient's HRQL.[75] Therefore, the QoL benefit of Efmody compared to glucocorticoid replacement therapy is demonstrated from

the sub-models where utility decrements, associated with comorbidities, are applied to a baseline utility. Swedish general population utilities reported by Lundberg (1998) were used as a baseline in the model.[100]
Each comorbidity reflected in the model had detrimental effects on patient HRQL. Therefore, each sub-model captured the utility decrement associated with the comorbidity. These were then combined multiplicatively to reflect the total impact of CAH on HRQL, when receiving Efmody or glucocorticoid replacement therapy, in each cycle. All HRQL impacts captured were measured using the EQ-5D questionnaire. The utility values applied in the model are summarised in Table 40.

Table 40. Base case health-related quality of life inputs

Sub-model	Health state	Utility	Reference	Notes
Adrenal crisis	Crisis	A one cycle decrement of 0.118 per crisis	NICE TA288[101]	Previously accepted for modelling adrenal crisis in Alkindi
Cardiovascular events	Angina	Utility multiplier of 0.764	Ara et al. (2010)[102]	
	Myocardial infarction	Utility multiplier of 0.764		
	Stroke	Utility multiplier of 0.658		
Fractures	Osteoporotic	Year 1 multiplier: 0.977 Year 2 multiplier: 1.000	Stevenson et al. (2007)[89]	Used in published health burden model[17]
	Hip	Year 1 multiplier: 0.792 Year 2 multiplier: 0.813		
	Vertebrae	Year 1 multiplier: 0.626 Year 2 multiplier: 0.909		
Obesity		Specific utility value for BMI units 18-40kg/m^2	Kearns et al. (2013)[103]	
Fertility	Infertility	Decrement of 0.006	NICE fertility guidelines[104]	Assumed to last for 36 months Used in published health burden model[17]
Diabetes		Per cycle decrement of 0.062	Sullivan et al (2011)[105]	Previously accepted for modelling adrenal crisis in Alkindi
Growth	<2 HSDS below gen pop.	Decrement of 0.01 per HSDSs	Christensen et al. (2007)[106]	Previously accepted for modelling adrenal crisis in Alkindi
	>2 HSDS below gen pop.	Decrement of 0.062 per HSDSs		

Key: BMI, body mass index; HSDS; height standard deviation score; NICE, National Institute for Health and Care Excellence

These comorbidities-associated disutilities were applied on the age-related utility values in the Danish general population, collected from Sorensen 2009. [100] The average EQ-5D-3L index value between male and female are presented in Table 41.

Table 41. Utility inputs – General population

Age	Utility values	Sources
20-29	0.931	Assumption: the same value as 20 years old
30-39	0.916	Sorensen 2009
40-49	0.895	Sorensen 2009

Age	Utility values	Sources
50-59	0.873	Sorensen 2009
60-69	0.861	Sorensen 2009
70-79	0.833	Sorensen 2009
80+	0.833	Assumption: the same value as 79 years old

Adrenal crises, CVD and diabetes are associated with increased mortality risk in the base case. The model also includes functionality to include mortality risk associated with obesity. More details are provided in the corresponding Sections below.

8.4.2 Health state utility values used in the health economic model

8.4.2.1 Adrenal crises

A simple decrement was applied each time a patient experienced an adrenal crisis. The TLR did not identify any studies reporting the HRQL impact of an adrenal crisis. However, the National Institute for Health and Care Excellence (NICE) technology appraisal (TA) 288 of dapagliflozin for treating T2DM reported a decrement of 0.118 for a glycaemic crisis.[101] The decrement was also accepted for modelling the HRQL impact associated with an adrenal crisis when the Nordic HTAs appraised Alkindi in paediatrics with AI.[18,149] This utility decrement and its relevance to adult CAH patients experiencing an adrenal crisis has been validated by clinical experts treating CAH patients in clinical practice.[12, 34]

8.4.2.2 Cardiovascular disease

It is assumed in the model that when a patient experiences a cardiovascular-related event it is either angina, a MI or a stroke. Utility multipliers for each of these events were sourced from the literature.[17] By using incidence data for the three types of cardiovascular event, a weighted utility multiplier was calculated and applied in the model for each patient experiencing a cardiovascular event. A conservative approach was taken to estimate the HRQL reductions due to CVD events: the loss of HRQL due to stroke, angina or MI was applied in the cycle of the event only, leading to an expected underestimate of the total QALY loss associated with these events.

The incidence and mortality of angina, MI, and stroke among Danish general population was taken from Danish Heart Statistics. Angina mortality was assumed to be zero based on the UK data, while mortality of MI and stroke was calculated by the number of cause-specific mortality divided by the number of case in Danish Heart Statistics.[145]

The incidence of CVD are shown in the Table 42.

Table 42. Cardiovascular disease – Incidence in general population

Gender	Age (years)	Angina (per 100,000 per year)	MI (per 100,000 per year)	Stroke (per 100,000 per year)
Female	18	0	0	0
	25	0	0	0
	35	18	42	58
	45	65	145	142
	55	144	317	263
	65	209	473	530
	75	228	668	1085
	85	283	1174	1901
Male	18	0	0	0
	25	0	0	0
	35	38	110	71
	45	142	369	205

	55	301	714	449
	65	430	1035	776
	75	446	1265	1318
	85	402	1785	2025
Key: MI Myocardial infarction Sources: Danish Heart Statistics				

Table 43. Cardiovascular disease – Case fatality rate in general population

Gender	Age (years)	Angina*	MI*	Stroke*
Female	18	0.000	0.000	0.000
	25	0.000	0.000	0.000
	35	0.000	0.000	0.000
	45	0.000	0.004	0.006
	55	0.000	0.004	0.009
	65	0.000	0.009	0.021
	75	0.000	0.020	0.044
	85	0.000	0.098	0.122
Male	18	0.000	0.000	0.000
	25	0.000	0.000	0.000
	35	0.000	0.008	0.007
	45	0.000	0.007	0.006
	55	0.000	0.010	0.011
	65	0.000	0.014	0.019
	75	0.000	0.027	0.041
	85	0.000	0.089	0.106
Key: MI Myocardial infarction Notes: *Case fatality rate is defined as the number of deaths associated with event divided by total number of events Sources: Danish Heart Statistics				

8.4.2.3 Bone health

Each fracture (osteoporotic, hip, and symptomatic vertebrae) is associated with a utility detriment that applies for the year immediately following the fracture. Hip and symptomatic vertebrae fractures are assumed to affect HRQL for more than a year. Another smaller decrement is applied in the second year to reflect the extended recovery period for these fractures. EQ-5D utility values were sourced from Stevenson et al. (2007).[89]Danish data were used for the risk of fracture in the general population. The fractures risk for CAH patients is calculated based on the risk of fracture in the general population and the relative risk for CAH population. On the top of it, an increased risk of fractures associated with the use of GC was considered.

Osteoporotic fractures were assumed to occur at the same rate as all non-vertebrae fractures and symptomatic vertebrae fractures were assumed to occur at the same rate as hip fractures based on the UK data. Age-specific incidence of non-vertebrae fracture was obtained from Driessen 2016.[146] Overall incidence and mortality of hip fracture were taken from Jantzen 2018[147] which were more conservative, and they were calculated based on the distribution of age groups from Driessen 2016 to derive the age-specific data.

Table 44. Fractures - Incidence in general population

Gender	Age (years)	Non-vertebrae*	Hip*
Female	18	0.010	0.001
	35	0.010	0.001
	45	0.014	0.001
	55	0.024	0.001
	65	0.031	0.001
	75	0.047	0.003
	85	0.090	0.005
Male	18	0.020	0.001

	35	0.014	0.001
	45	0.015	0.001
	55	0.014	0.001
	65	0.016	0.001
	75	0.024	0.001
	85	0.055	0.002
Sources: Non-vertebrae fracture from Driessen 2016, hip fracture from Jantzen 2018 and calculated based on the distribution of age groups in Driessen 2016. *Incidences calculated from published fracture incidence per 100,000 values.			

Table 45. Fractures – Hip mortality risk

Age (years)	Mortality risk
<50	0.000
50-60	0.077
60-70	0.231
70-80	0.231
80-90	0.423
90+	0.616
Sources: Jantzen 2018 calculation based on the distribution in the UK data.	

8.4.2.4 Obesity

Numerous studies relating HRQL with BMI were identified by targeted literature research. Three studies that capture the relationship between EQ-5D utility scores and BMI were included in the model. Sach et al. (2007) reported utility scores associated with each BMI band, defined by the World Health Organization.[107] Macran et al. (2004) reported a utility decrement of 0.0033 for every unit of BMI above 21kg/m^2.[108] Finally, Kearns et al. (2013) reported utility values for BMI units 18–40kg/m^2.[103] The data extracted from Kearns et al. (2013) are used in the base case analysis as the utilities for individual BMI units reported meant results were more responsive to change than when using the results reported in Sach et al. (2007),[103, 107] where utility scores were given for five-unit increments. Kearns et al. (2013) also provided more recent data than Macran et al., which used data from the 1996 Health Survey for England.[103, 108] The alternative sources to estimate HRQL associated with BMI were explored in scenario analysis.

To estimate the BMI of the patients in the model, the BMI from the general population was estimated from the height and the weight of the Danish population between 0 and 24 years old (Tinggaard 2013) [135] and extrapolated using the UK distribution for the patients older than 24 years old. Then, the age-specific BMI calculated for Danish general population was multiplied by 1.23 based on Arlt et al. 2010[10] (same multiplier for males and females) in order to reflect the BMI of the CAH population.

By providing physiological cortisol replacement, Efmody has potential to remove the increased risk of obesity due to CAH and according to the expert it is reasonable to assume that patient's BMI will reduce over 12 months when treated with Efmody.

Table 46. Weight, height, BSA and BMI of Danish general population

Age (years)	Weight (kg)		Height (cm)		BSA (m^2)		BMI (kg/ m^2)	
	Male	Female	Male	Female	Male	Female	Male	Female
0	14.12	13.92	55.73	54.02	0.47	0.46	45.48	47.70
1	19.69	18.87	77.27	75.21	0.65	0.63	32.98	33.35
2	21.55	20.93	88.21	86.50	0.73	0.71	27.69	27.97
3	23.61	23.20	97.44	95.73	0.80	0.79	24.87	25.31
4	25.46	25.26	104.62	103.93	0.86	0.85	23.27	23.38
5	27.73	27.53	111.79	111.45	0.93	0.92	22.19	22.16
6	29.79	29.59	119.66	117.95	1.00	0.98	20.81	21.27
7	32.47	31.65	125.81	124.10	1.07	1.04	20.52	20.55
8	35.15	34.54	131.97	129.57	1.14	1.11	20.19	20.57
9	38.45	37.42	137.44	136.07	1.21	1.19	20.36	20.21

10	41.55	40.72	142.56	141.88	1.28	1.27	20.44	20.23
11	45.05	43.81	148.72	147.69	1.36	1.34	20.37	20.09
12	48.97	47.73	154.53	152.82	1.45	1.42	20.51	20.44
13	53.71	51.44	161.03	157.27	1.55	1.50	20.71	20.80
14	58.45	54.74	166.84	161.03	1.65	1.56	21.00	21.11
15	63.61	58.04	171.97	164.10	1.74	1.63	21.51	21.55
16	68.14	60.93	175.73	166.50	1.82	1.68	22.07	21.98
17	72.06	63.81	178.46	168.21	1.89	1.73	22.63	22.55
18	74.95	66.29	180.51	169.23	1.94	1.77	23.00	23.15
19	76.39	68.76	181.20	168.89	1.96	1.80	23.27	24.11
20-24	77.63	71.03	181.20	169.23	1.98	1.83	23.64	24.80
25-34	81.91	75.49	181.94	168.57	2.03	1.88	24.75	26.57
35-44	84.57	77.05	180.01	168.47	2.06	1.90	26.10	27.15
45-54	87.12	78.50	179.39	167.54	2.08	1.91	27.07	27.97
55-64	87.12	76.95	177.66	166.81	2.07	1.89	27.60	27.65
65-74	84.67	75.91	176.24	164.54	2.04	1.86	27.26	28.04
75+	79.75	70.09	173.08	160.93	1.96	1.77	26.62	27.06
Source	Data in 0-24 years old are from Tinggaard 2013: Data in the rest of age groups are calculated based on the distribution of age group data in the UK[90]				Body surface area (BSA, m^2) = (height (cm) x weight (kg)/3600)½		BMI (m^2) = weight (kg) / height (cm)^2	

8.4.2.5 Fertility

A utility decrement in line with that used in the NICE fertility guidelines is included in the fertility sub-model to capture the HRQL loss associated with infertility.[104] However, the duration of this decrement is uncertain. In the CAH burden of illness report by Hummel et al. (2016), the decrement was applied for the remainder of the time horizon.[17] A more conservative assumption is made in the model, with the decrement enduring for 3 years in the base case analyses. The 3-year period begins when the age of patients reaches 28.6 years, the average age of parents in Denmark.[132, 146]

8.4.2.6 Diabetes

A utility decrement associated with diabetes (type 2), reported by Sullivan et al. (2011), of 0.062 per cycle is incorporated into the model.[105] This approach was accepted in previous appraisal of Alkindi. [18,149] Note that disutility due to gestational diabetes on mother and infant has not been modelled.

Table 47. Sub-model incidence and clinical efficacy parameters - diabetes

Parameter	Incidence per 100,000	Source / Comment
Diabetes incidence: 10-14 (years)	52	Carstensen 2020, calculation based on the distribution in the UK data
Diabetes incidence: 15-19 (years)	111	
Diabetes incidence: 20-39 (years)	233	
Diabetes incidence: 40-59 (years)	1196	
Diabetes incidence: 60+ (years)	1472	
Diabetes OR Female SOC	4.00	
Diabetes OR Male SOC	2.10	
Diabetes death HR	1.80	Falhammar et al. 2015[41]
Diabetes HR: <5mg dose	1.90	
Diabetes HR: <15mg dose	2.19	Seshasai et al. 2011[99]
Diabetes HR: <25mg dose	3.33	Wu et al. 2020[98]
Diabetes HR: >25mg dose	4.34	

8.4.2.7 Height

The clinical expert agreed that this value reflect what is expected in the clinical practice for patients receiving standard of care.

A study by Christensen et al. (2007) reported a correlation between below-average height and reduced HRQL.[106] Models predicting EQ-5D utility scores were fitted to data for patients above average height, <2 HSDs below general population average and >2 HSDs below general population average height. The model coefficients suggest patients <2 HSDs below general population average height experience a decrement of 0.01 per HSD. Patients >2 HSDs below general population average height experienced a decrement of 0.061 per HSD. This approach was accepted for Alkindi.[18,149]

The estimated height values applied in the model are presented in Table 46. Impact of a minor potential difference in the height reduction to the model outcome is minor (tested as part of the Scenario Analysis); hence, presented value was deemed acceptable.

8.5 Resource use and costs

8.5.1 Treatment costs

Adult patients begin treatment on Efmody with a dose of 30mg per day, which can be reduced over time if the clinician believes their hormone levels can be controlled at a lower dose. In DIUR-006, doses were reduced to a mean dose of [redacted] per day (median dose of 20mg per day), over a 12-month period, where the dose remained stable for the remainder of the follow-up time for over 3.5 years. Because Efmody is only available in 5mg increments, setting the final dose to [redacted] would overestimate the cost and underestimate the effect (as a cost for 25mg per day would be incurred). To overcome this, the model assumes that [redacted] of patients reduce their dose to [redacted]% of patients receive a [redacted] dose to result in an estimated mean of [redacted] in line with the DIUR-006 trial.[30] Patients remain on this dose for their lifetime. Efmody is available in 5mg and 10mg doses, with a uniform list price of PPP DKK 4.50 per mg (average PSP DKK 6.30 per mg,

Table 49). The drug costs applied in the primary cost-effectiveness model are outlined in Table 48. Parameters related to drug costs were taken from national list of prices (Danish Medicines Agency).

In the model, the comparator treatment is formed of a basket of therapies, informed by clinical guidelines and clinical opinion.[11, 54] Clinicians reported the treatments they prescribed for their adolescent (aged ≥12 years) and adult patients with CAH, the proportion of their patients they prescribed each therapy to, and an estimate of the average dose. For the base case, two clinicians practicing in Sweden were interviewed and the average of the values provided taken (assumptions have not been validated by a Danish endocrinologist). The resulting basket of therapies that constitutes the comparator arm and the treatment costs is reported in Table 48.

Efmody daily and annual cost per patient are higher than corresponding cost of hydrocortisone immediate-release tablets, Plenadren (only used for adults) and Prednisolone, but Efmody daily and annual cost per patient is lower than Alkindi (only used for adolescents).

Adolescents with CAH require a lower dose of glucocorticoids to control their cortisol and androgen levels. Data from the I-CAH Registry reports patients aged 12-18 receive a median glucocorticoid dose of 14.0 (11.6–17.4) mg/ m^2/ day. For simplicity, the model assumes adolescent patients on glucocorticoid replacement therapy receive a dose of 50% of the adult dose for each glucocorticoid type. This assumption has been validated by a clinician practicing in Denmark and was deemed to reflect clinical practice. Limited data has been collected to inform the dose of Efmody that would be most suitable for adolescents. An analysis of the range of doses by body surface area for patients that are still growing, shows that the range of dose 10-15mg/m^2/day can be recreated with Efmody.[110] Therefore, it has been assumed that patients would receive 15mg. Once becoming suitable for adult dosing, patients would be increased immediately to the user-amendable final adult dose (mean dose of [redacted]). In the model, the age at which patients move onto the adult dose is when they are assumed to finish growing, at approximately 16 years old.[63] Table 51 reports the dose used in the model. The inputs and assumptions regarding adolescent dosing have been validated by clinical experts as part of the model validation meetings.[54, 12]

When there are more than one dosing packages for one comparator, the package whose unit dose is close to daily dose were selected and the average cost per mg were calculated to populate the CE model. Average Apotekernes

Indkøbspris (AIP) excluding value added tax (VAT) of each comparator was taken from Danish Medicines Agency MEDICINPRISER.DK. [148] Detailed costs of the selected products are presented in Appendix K.

Table 48. Primary model costs (PPP): Drug acquisition - Average cost per mg (all medications)

CAH medication (Adults)						
Treatment	**Average cost per mg (DKK)**	**Unit dose (mg)**	**Daily dose (mg)**	**Cost per one month cycle (DKK)**	**Percentage usage**	**Source**
Hydrocortisone	0.10	10	30	72.35	77%	MEDICINPRISER .DK - 2021/9/08
	0.07	20				
Plenadren	7.17	5	30	4,379.33	20%	
	3.61	20				
Prednisolone	0.08	5	5	11.69	3%	
CAH medication (Adolescents)						
Treatment	**Average cost per mg (DKK)**	**Unit dose (mg)**	**Daily dose (mg)**	**Cost per one month cycle (DKK)**	**Percentage usage**	**Source**
Hydrocortisone	0.10	10	15	44.84	82.00%	MEDICINPRISER .DK - 2021/9/08
	0.07	20				
Prednisolone	0.08	5	5	5.85	3%	
Alkindi	13.28	1, 2 or 5	15	822.57*	15.00%	

Table 49. Primary model costs: Efmody List prices, per pack and per mg

Product, strength		**PPP per pack, DKK**	**PSP per pack, DKK**	**PPP per mg, DKK**	**PSP per mg, DKK**
(pack size)	**mg/pack**				
Efmody 5mg, 50	250	1,125.56	1,530.70	4.50	6.12
Efmody 10 mg, 50	500	2,251.11	3,044.60	4.50	6.09
		per mg		**4.50**	**6.11**

Notes: Efmody 5 mg: PSP =10+(1.25*(1,125.56*0.076+1,125.56+5.46)). PSP rounded =1,530.70; Efmody 10 mg: PSP = =10+(1.25*(2,251.11*0.076+2,251.11+5.46)). PSP rounded =3,044.60. Only glucocorticoid therapies used as monotherapies are included in the model. Dexamethasone, which is used in combination with hydrocortisone, is not considered in the model.
Source for prices: https://laegemiddelstyrelsen.dk/da/tilskud/priser/omregning-til-forbrugerpris/

The average cost of Efmody per day for the treatment of CAH in adolescents and adults, respectively, is presented in Table 50.

Table 50. Primary model costs: Efmody List prices, average daily cost (in DKK)

	AIP (PPP)	**AUP (PSP)**
Daily cost age ≥ 12 <18 years (assume daily dose: 15mg):	67.50	91.65
Daily cost age ≥18 years (assume daily dose: 20mg):	90.00	122.20

During illness and situations of stress (e.g. major surgery or trauma), all patients with CAH need to increase their dose of medication to meet the natural increased demand on cortisol (known as sick day rules/dosing).[11] The trial data also demonstrated that Efmody reduced sick day rules usage; in DIUR-005, AEs leading to use of sick day rules were reported more often in the glucocorticoid replacement therapy group compared with the Efmody group (36 [59.0%] versus 26 [42.6%] patients; total of 96 AEs versus 68 AEs, respectively), despite similar overall rates of intercurrent illness.[28] Sick day rules are discussed in more detail in Section 7.1.4.7.

Sick day dosage in the Efmody arm reflects the approach taken in DIUR-005. Patients were instructed to take three 20mg doses of immediate-release hydrocortisone for the duration of the sick day event.[28] The procedure for the comparator arm was informed by clinical opinion to reflect clinical practice. All clinicians agreed they would have instructed their patients to take an additional number of doses of immediate-release hydrocortisone each day; the number of additional doses varied with a mean of three, which was used in the model. It was assumed that all sick day events lasted for 3 days, based on clinical opinion.[12, 34, 54] Sick day dosage for adolescents receiving Efmody have not been outlined and the doses prescribed for adults would be excessive for the adolescent population. Therefore, it was assumed that Efmody patients would receive half the sick day dose an adult receives. This is reflective of the ratio of adolescent to adult starting dose for Efmody, 15mg for adolescents compared to 30mg for adults. The sick day dose, which adolescent patients receive will be varied in scenario analysis.

In the model, it is assumed that patients in the Efmody arm experienced two sick day periods a year, while patients in the comparator arm experienced three. Clinical experts believed this assumption was plausible when interviewed as part of clinical validation.[12, 34] Cost of immediate-release hydrocortisone was used for sick day dosing.

8.5.1.1 Sick day rules

During illness and situations of stress (e.g. major surgery or trauma), all patients with CAH need to increase their dose of medication to meet the natural increased demand on cortisol (known as sick day rules/dosing).[11] The trial data also demonstrated that Efmody reduced sick day rules usage; in DIUR-005, AEs leading to use of sick day rules were reported more often in the glucocorticoid replacement therapy group compared with the Efmody group (36 [59.0%] versus 26 [42.6%] patients; total of 96 AEs versus 68 AEs, respectively), despite similar overall rates of intercurrent illness.[28]

Sick day dosage in the Efmody arm reflects the approach taken in DIUR-005. Patients were instructed to take three 20mg doses of immediate-release hydrocortisone for the duration of the sick day event.[28] The procedure for the comparator arm was informed by clinical opinion to reflect clinical practice. All clinicians agreed they would have instructed their patients to take an additional number of doses of immediate-release hydrocortisone each day; the number of additional doses varied with a mean of three, which was used in the model. It was assumed that all sick day events lasted for 3 days, based on clinical opinion.[12, 34, 54] Sick day dosage for adolescents receiving Efmody have not been outlined and the doses prescribed for adults would be excessive for the adolescent population. Therefore, it was assumed that Efmody patients would receive half the sick day dose an adult receives. This is reflective of the ratio of adolescent to adult starting dose for Efmody, 15mg for adolescents compared to 30mg for adults. The sick day dose, which adolescent patients receive will be varied in scenario analysis.

In the model, it is assumed that patients in the Efmody arm experienced two sick day periods a year, while patients in the comparator arm experienced three. Clinical experts believed this assumption was plausible when interviewed as part of clinical validation.[12, 34] Cost of immediate-release hydrocortisone was used for sick day dosing.

8.5.1.2 Healthcare resource use

Patients with CAH require numerous tests and appointments with medical staff each year to ensure patients are receiving the correct treatment and, during adolescence, they are developing safely. No literature was identified in the SLR to inform the frequency of tests, medical appointments or associated costs in the model. Therefore, estimates based on clinical interviews with endocrinologists were used.[54] As no Danish clinical experts were included in the clinical interviews, the resource use from one Norwegian endocrinology was applied in the Danish setting. The resource use estimated used in the model are presented in Table 51.

The simplified Efmody treatment regimen is easy-to-remember and implement, and will lead to improved patient adherence; optimal disease control will also eliminate the need for time sensitive sampling, reducing the burden of disease monitoring and dose titration resulting in reduced healthcare resource use. This assumption was validated by clinical experts.[54, 12]

Resource use for the Efmody arm is incorporated in the model as a 15% reduction in the resource use on glucocorticoid replacement therapy, informed by clinical opinion.[54] This value is explored in sensitivity analysis.

The model requires to be filled with cost per hour for visits. In the absence of Danish value, the UK costs per hour were converted into Danish currency (using the average exchange rate over six months from the Denmark National Bank). The durations of the visit to each healthcare providers were provided by the expert for Danish settings. Then

these two parameters were multiplied together to obtain an estimation of the cost per visit. Then it was further multiplied by the number of visits per year and the percentage of patients concerned.
The assumption of using some UK costs for visits is conservative as unit costs in Denmark are higher than in the UK, so it will overestimate the ICER.

Table 51: Monitoring costs and frequencies – health care professionals

Medical professional	Unit cost (DKK)	Adolescents		Adults		Price references
		% of patients	Visits per year	% of patients	Visits per year	
Nurse	284	0%	0	0%	0	Costs in the regionerne in 2018, Sygehjælpere, inflated to 2021
Endocrine specialist nurse	240	10%	1	0%	0	SalaryExpert's Salary Assessor Platform, nurse specialist
Community nurse	236	0%	0	0%	0	SalaryExpert's Salary Assessor Platform, community health nurse
Practice nurse	237	0%	0	0%	0	SalaryExpert's Salary Assessor Platform, medical licensed practical nurse
GP	661	10%	1	0%	0	SalaryExpert's Salary Assessor Platform, physician general practice
Primary care physician	567	10%	1	1%	0	Takstkort, Intern Medicin, 0110, 1. konsultation,0120,2. konsultation
Endocrinologist	650	100%	2	4%	1	SalaryExpert's Salary Assessor Platform, medical endocrinologist
Surgeon	306	10%	1	0%	0	Takstkort, Kirurgi, 0110,1. konsultation, 0130, Senere konsultation
Psychologist	403	20%	1	10%	1	Takstkort, Psykiatri, 0205, Telefonisk rådgivning/rådgivning per edifact til lægelige samarbejdspartnere
Gynaecologist	558	0%	0	25%	1	Takstkort, Gynækologi og obstetrik, 0110,1. konsultation, 0130, Senere konsultation

Source: Prices are based on the Denmark DRG tariff 2021, mainly from Association of Specialists (FAS) and the Regions' Wage and Tariff mention https://www.laeger.dk/takstkort**.** In the absence of data from official sources recommended by the DMC guidelines, other sources as described were used.

Table 52: Monitoring costs and frequencies – Tests

Resource	Cost (DKK)	Glucocorticoid replacement therapy– Tests per year		Efmody – Tests per year		Cost Source
		Adolescents	Adults	Adolescents	Adults	
Blood test	1,102	2.00	0.00	1.70	0.00	Rigshospitalets Labportal and Laboratorieundersøgelser-7166 B
Bone age	278	0.00	1.00	0.00	0.85	Takstkort, Radiologi, 2110
Blood pressure	398	2.00	1.00	1.70	0.85	Takstkort, Intern Medicin, 2213, Døgnblodtryksmonitering
Screening for TARTs in male	596	0.00	0.06	0.00	0.02	Takstkort, Radiologi, 2154, Ultralydsundersøgelse af de mandlige kønsorganer (srotum)
BMD test	278	0.00	0.20	0.00	0.17	Takstkort, Radiologi, 2130

Key: BMD, bone mineral density; TART, testicular adrenal rest tumours https://labportal.rh.dk/Metodeliste.asp?Page=1 and Association of Specialists (FAS) and the Regions' Wage and Tariff mention - Laboratorieundersøgelser https://www.laeger.dk/sites/default/files/generellelaboratorieundersoegelser_takstkort_pr_040121.pdf

8.5.1.3 Sub-model costs

The unit costs for the healthcare resource use and sub-models are identified from several sources (7): Further detail on the modelling approach and assumptions made in each sub-model are presented below.

An assumption that there is no cost associated with managing obesity or height is made in the model. This assumption was previously made and accepted for the Alkindi appraisal.[18,149] The cost associated with each comorbidity has been derived from literature sources and clinical interviews.[54]

The selected codes in the DRG lists and the detailed calculation of costs from published literature are presented in the Tables below (Tables 56-61).

In the absence of local costs, average exchange rate over six months from the Denmark National Bank[144] was used to convert the UK cost value into Danish cost value. This assumption was considered as conservative as the UK price level of heath care is significantly lower than that in Denmark.

Table 53: Sub-model costs

Crisis			
Resource	**Value (2020-2021 price year, DKK)**	**Proportion**	**Source**
Adrenal Procedures with CC Score 2+	67,554	0.75	Takstkort, Radiologi, 2110, Røntgenundersøgelse af hånd og/eller håndled
Adrenal Procedures with CC Score 0-1	21,801	0.25	Takstkort, Radiologi, 2130, Røntgenundersøgelse af bækken, 2304, Bevægelse og funktionsoptagelse af rygsøjle
Total cost per crisis	56,116		Calculation based on the unit costs and proportion
Micro costing			
Resource	**Value (2020-21 price year, DKK)**	**Proportion**	**Source**
Emergency services	285	0.75	70AK01,Lette akutte kontakter
A&E admission	1,542	1.00	UK value converted to DKK

Overnight stay in hospital	602	0.75	Genoptræningstakster 2021, lønsumstakster og -afgifter (Excel),Taksten for langliggere,Langligger Takstkort, Radiologi, 2110, Røntgenundersøgelse af hånd og/eller håndled
Day case	135	0.25	Takstkort, Radiologi, 2110, Røntgenundersøgelse af hånd og/eller håndled
Intensive care	396,359	0.10	26MP08,Intensiv gruppe IV: Alvorligt multiorgansvigt,26MP09,Intensiv gruppe III: Tiltagende alvorligt organsvigt i flere organer,26MP10,Intensiv gruppe II: Tiltagende alvorligt organgsvigt i et organ,26MP11,Intensiv gruppe I: Simpelt organsvigt i et eller to organer
Ventilation	10,300	0.01	04MP12,Andre sygdomme i luftveje, udredning
Cardiopulmonary support	5,353	0.01	05SP01,Sammedagspakke: Lille Cardiologisk sammedagsudredningspakke,05SP02,Sammedagspakke: Mellem Cardiologisk sammedagsudredningspakke,05SP03,Sammedagspakke: Stor Cardiologisk sammedagsudredningspakke
X-ray	505	0.50	30PR18,Røntgenundersøgelse (alm), ukompliceret
Additional glucocorticoids	31	1.00	MEDICINPRISER.DK - 2021/4/06
Fluids	43,115	1.00	08MA12,Generaliserede bindevævssygdomme
Hydrocortisone IV (on arrival)	3,100	1.00	UK value (KB04Z - Continuous Subcutaneous Insulin Infusion) converted to DKK
Hydrocortisone drip (daily)	3,100	0.25	UK value (KB04Z - Continuous Subcutaneous Insulin Infusion) converted to DKK
Total cost per adrenal crisis	53,381		Calculation based on the unit costs and proportion
Cardiovascular Disease			
Event	**Value (2020-21 price year, DKK)**		**Source**
Angina	17,507		05MA03,Stable ischemic heart disease / chest pain,05MP38,Stable ischemic heart disease, procedure group. B and / or C,05MP39,Stable ischemic heart disease or congenital heart disease, pat at least 15 years, procedure group. A
Myocardial infarction	49,322		05MA01,Akut myokardieinfarkt med ST-segment elevation,05MP32,Akut myokardieinfarkt med ST-segment elevation, proceduregrp. C,05MP33,Akut myokardieinfarkt med ST-segment elevation, proceduregrp. B,05MP34,Akut myokardieinfarkt med ST-segment elevation, proceduregrp. A
Stroke	32,320		01MP11,Trombolysebehandling af akut apopleksi
Fractures			
Fracture	**Value (2020-21 price year, DKK)**		**Source**
Osteoporotic	38,603		08MA03,Konservativ behandling af brud og ledskred i ekstremiteterne, pat. Mindst 18 år,08MA04,Konservativ behandling af brud og ledskred i ekstremiteterne, pat. 0-17 år,08MP23,Frakturkirurgi, skulder/overarm,08MP24,Frakturkirurgi, albue/underarm,08MP25,Frakturkirurgi, håndled,08MP26,Frakturkirurgi, hånd,08MP27,Frakturkirurgi, ekstern fiksation, underekstremitet ekskl. fod,08MP29,Frakturkirurgi, intern fiksation, lår,08MP30,Frakturkirurgi, intern fiksation, knæ/underben,08MP31,Frakturkirurgi, intern fiksation, ankel,08MP32,Frakturkirurgi, fod
Hip	47,223		08MA01,Konservativt behandlet brud i bækken og lår,08MP28,Frakturkirurgi, intern fiksation, hoftenær
Vertebrae	90,959		08MA02,Konservativt behandlet patologisk fraktur

Fertility		
Resource	**Value (2020-21 price year, DKK)**	**Source**
Cost per cycle of IVF	24,167	Aagaard klinik,IVF treatment,Dansk Fertilitetsklinik,Basic IVF treatment,Trianglen Fertility Clinic,Single cycle any age
Cost of unassisted pregnancy (antenatal, intrapartum and postnatal care)	38,946	09MP03,Stor mammakirurgisk operation,09MP05,Lille mammakirurgisk operation,14MA02,Indlæggelser i barselsperioden
Sperm extraction	3,833	Aagaard klinik,Extra charge for surgical extraction of sperm (TESA),Dansk Fertilitetsklinik,Testicular sperm extraction,Trianglen Fertility Clinic,TESA - aspiration of sperm cells from testicles for use with ICSI
Diabetes		
Resource	**Value (2020-21 price year, DKK)**	**Source**
Overall management cost	23,967	Sortsø 2015, cost year 2011, inflated to 2021
Key: A&E, accident and emergency; IV, intravenous; IVF, *in vitro* fertilization Source: The costs were derived from DRG code in Denmark DRG tariff 2021 https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2021		

8.5.1.3.1 Adrenal crisis

Two approaches for modelling the costs associated with an adrenal crisis were included in the model; a micro-costing approach and a directly reported cost. The micro-costing used resource use data collected during clinical interviews, the cost associated with each resource was then sourced from literature sources, or UK values were used in absence of Danish specific cost data (Table 58). This was considered most reflective of clinical practice and so was used in the base case. An adrenal procedure was split into two categories: clinical coding (CC) score 0–1 or ≥2. A single cost per crisis was calculated by deriving a weighted average. When the interviewed clinicians had been asked to estimate the percentage of patients who would have to spend the night in hospital following an AC, it was assumed those staying overnight (75%) would require an adrenal procedure with CC score ≥2. The percentage of patients requiring overnight care is varied as part of scenario analysis.

Table 54: Sub-model costs – adrenal crisis

Crisis			
Resource	**Value (2020-2021 price year, DKK)**		**Source**
Adrenal Procedures with CC Score 2+	67554		Takstkort, Radiologi, 2110, Røntgenundersøgelse af hånd og/eller håndled
Adrenal Procedures with CC Score 0-1	21801		Takstkort, Radiologi, 2130, Røntgenundersøgelse af bækken, 2304, Bevægelse og funktionsoptagelse af rygsøjle
Micro costing			
Resource	**Value (2020-21 price year, DKK)**	**Proportion**	**Source**
Emergency services	285	0.75	70AK01,Lette akutte kontakter
A&E admission	1,542	1.00	UK value converted to DKK

Overnight stay in hospital	602	0.75	Genoptræningstakster 2021, lønsumstakster og -afgifter (Excel),Taksten for langliggere,Langligger Takstkort, Radiologi, 2110, Røntgenundersøgelse af hånd og/eller håndled
Day case	135	0.25	Takstkort, Radiologi, 2110, Røntgenundersøgelse af hånd og/eller håndled
Intensive care	396,359	0.10	26MP08,Intensiv gruppe IV: Alvorligt multiorgansvigt,26MP09,Intensiv gruppe III: Tiltagende alvorligt organsvigt i flere organer,26MP10,Intensiv gruppe II: Tiltagende alvorligt organgsvigt i et organ,26MP11,Intensiv gruppe I: Simpelt organsvigt i et eller to organer
Ventilation	10,300	0.01	04MP12,Andre sygdomme i luftveje, udredning
Cardiopulmonary support	5,353	0.01	05SP01,Sammedagspakke: Lille Cardiologisk sammedagsudredningspakke,05SP02,Sammedagspakke: Mellem Cardiologisk sammedagsudredningspakke,05SP03,Sammedagspakke: Stor Cardiologisk sammedagsudredningspakke
X-ray	505	0.50	30PR18,Røntgenundersøgelse (alm), ukompliceret
Additional glucocorticoids	31	1.00	08MA12,Generaliserede bindevævssygdomme
Fluids	43,115	1.00	UK value converted to DKK
Hydrocortisone IV (on arrival)	3,100	1.00	UK value converted to DKK
Hydrocortisone drip (daily)	3,100	0.25	UK value converted to DKK
Total cost per adrenal crisis	**53,381**		Calculation based on the unit costs and proportion

8.5.1.3.2 Cardiovascular events

The approach used to model the cost of a cardiovascular event is similar to the one used to derive the associated utility. It is assumed that a cardiovascular event is either angina, a MI or a stroke. The incidence rates of these three events are presented in Table 42, along with the Danish cost associated with each event (Table 59), are used to calculate a weighted average cost of cardiovascular events.[113,136] The cost of a cardiovascular event is applied as a one-off cost for patients experiencing cardiovascular disease. A conservative approach was taken to estimate the cost impact due to CVD events: the cost impact was applied in the cycle of the event only, leading to an expected underestimation of total costs associated with these events.
The cost used for in the model for treating different cardiovascular events are presented in Table 59.

Table 55: Cardiovascular events – Costs

Crisis		
Resource	**Value (2020-2021 price year, DKK)**	**Source**
Adrenal Procedures with CC Score 2+	67554	Takstkort, Radiologi, 2110, Røntgenundersøgelse af hånd og/eller håndled
Adrenal Procedures with CC Score 0-1	21801	Takstkort, Radiologi, 2130, Røntgenundersøgelse af bækken, 2304, Bevægelse og funktionsoptagelse af rygsøjle
Micro costing		

Resource	Value (2020-21 price year, DKK)	Proportion	Source
Cardiovascular Disease			
Event	**Value (2020-21 price year, DKK)**		**Source**
Angina	17,507		05MA03,Stable ischemic heart disease / chest pain,05MP38,Stable ischemic heart disease, procedure group. B and / or C,05MP39,Stable ischemic heart disease or congenital heart disease, pat at least 15 years, procedure group. A
Myocardial infarction	49,322		05MA01,Akut myokardieinfarkt med ST-segment elevation,05MP32,Akut myokardieinfarkt med ST-segment elevation, proceduregrp. C,05MP33,Akut myokardieinfarkt med ST-segment elevation, proceduregrp. B,05MP34,Akut myokardieinfarkt med ST-segment elevation, proceduregrp. A
Stroke	32,320		01MP11,Trombolysebehandling af akut apopleksi

The costs are from DRG code in Denmark DRG tariff 2021 https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2021; https://fred.stlouisfed.org/series/DNKCPICORMINMEI to adjust the inflation

8.5.1.3.3 Bone health

The cost of fracture is incurred as a one-off cost in the cycle at the time the fracture occurred. The cost of treating hip, symptomatic vertebrae and forearm fractures presented in Table 59.

Table 56: Fractures - Costs

Fractures		
Fracture	**Value (2020-21 price year, DKK)**	**Source**
Osteoporotic	38,603	08MA03,Konservativ behandling af brud og ledskred i ekstremiteterne, pat. Mindst 18 år,08MA04,Konservativ behandling af brud og ledskred i ekstremiteterne, pat. 0-17 år,08MP23,Frakturkirurgi, skulder/overarm,08MP24,Frakturkirurgi, albue/underarm,08MP25,Frakturkirurgi, håndled,08MP26,Frakturkirurgi, hånd,08MP27,Frakturkirurgi, ekstern fiksation, underekstremitet ekskl. fod,08MP29,Frakturkirurgi, intern fiksation, lår,08MP30,Frakturkirurgi, intern fiksation, knæ/underben,08MP31,Frakturkirurgi, intern fiksation, ankel,08MP32,Frakturkirurgi, fod
Hip	47,223	08MA01,Konservativt behandlet brud i bækken og lår,08MP28,Frakturkirurgi, intern fiksation, hoftenær
Vertebrae	90,959	08MA02,Konservativt behandlet patologisk fraktur

8.5.1.3.4 Fertility

The cost of pregnancy, including antenatal, intrapartum and postnatal care, is associated with each successful conception. The cost was reported in the NICE fertility costing report 2013 and has been inflated to the 2019 price level using the inflation indices reported in the PSSRU 2020.[104, 112] A separate cost associated with assisted conceptions is also included in the model. All assisted conceptions are assumed to include three rounds of *in vitro* fertilisation (IVF), and male patients receiving assisted conception also incur the cost associated with surgical sperm extraction. The resource use required to manage CAH patients trying to conceive has been informed by panel of seven European endocrinologists (including endocrinologists from Sweden and Norway). [12, 54]

The same approach was used as in the core UK model to capture fertility in the Danish model except that Danish specific data were applied for the age of attempted conception – 28.6 years (based on Statistics Denmark) [132]. The costs applied to the model are presented in Table 57.

Table 57: Fertility – Costs (IVF costs and postnatal care)

Fertility		
Resource	**Value (2020-21 price year, DKK)**	**Source**
Cost per cycle of IVF	24,167	Aagaard klinik,IVF treatment,Dansk Fertilitetsklinik,Basic IVF treatment,Trianglen Fertility Clinic,Single cycle any age
Cost of unassisted pregnancy (antenatal, intrapartum and postnatal care)	38,946	09MP03,Stor mammakirurgisk operation,09MP05,Lille mammakirurgisk operation,14MA02,Indlæggelser i barselsperioden
Sperm extraction	3,833	Aagaard klinik,Extra charge for surgical extraction of sperm (TESA),Dansk Fertilitetsklinik,Testicular sperm extraction,Trianglen Fertility Clinic,TESA - aspiration of sperm cells from testicles for use with ICSI

8.5.1.3.5 Diabetes

A study by Ara (2004) reported the cost of managing diabetes for 6 months.[114] This value has been inflated to the latest price year (2019) and used to calculate a monthly cost of managing diabetes. This approach was accepted for Alkindi assessment for paediatric AI.[18,149] As this reference is from 2004, it is likely that this cost underestimates the true cost of treating diabetes given the additional treatments which are currently used. For simplicity, costs due to gestational diabetes, such as risk of caesarean section and neonatal intensive care, have not been modelled.
The monthly cost for the treatment and management of type II diabetes was taken from Sortsø et al (2015) [130] (Table 58) and was inflated to cost year of 2021.

Table 58: Diabetes – Costs

Diabetes		
Resource	**Value (2020-21 price year, DKK)**	**Source**
Overall management cost	8,631	Sortsø 2015, cost year 2011, inflated to 2021

8.6 Results

8.6.1 Base case overview

The key assumptions made in the economic model are summarised in Table 59.

Table 59: Key modelling assumptions

Category	Assumption	Justification
Treatment effect	Efmody negates the risk of comorbidities associated with unphysiological cortisol and uncontrolled androgen levels.	Efmody provides physiological cortisol replacement resulting in controlled androgen levels. Therefore, a CAH patient receiving Efmody would be expected to have normalised cortisol and androgen levels reflective of the general population.
	In the cardiovascular disease, bone health, obesity, diabetes and height sub-models Efmody benefits patients through both the reduction of glucocorticoid dose and the normalisation of cortisol and androgen levels.	Clinical opinion from seven clinical experts validated that CAH patients would benefit from a reduction in glucocorticoid dose, in addition to normalised cortisol and androgen levels
Adolescent population dosing	Adolescents receive a 15mg-per-day dose of Efmody and a 50% reduction in adult dose for glucocorticoid replacement therapy.	There is currently limited evidence for Efmody in the adolescent population. The adolescent dose is based on clinical opinion.
	Adolescents move onto the adult dose when they finish growing. In the model female patients finish	Once a patient has finished growing, they would be expected to require a higher dose of Efmody or

Category	Assumption	Justification
	growing at 15.9 years old and male patients at 16.6, based on a study by Pijnenburg-Kleizen et al.[63]	glucocorticoid replacement therapy to manage their cortisol and androgen levels.
Adrenal crisis	The frequency of adrenal crises reported in adults with CAH is applicable to the adolescent population.	Data on adrenal crisis frequency in adolescents is not available for the Efmody clinical trials and is under-reported in the literature. The validity of the use of the adult trial data to inform the adolescent licence was supported by the development of a human physiologically based pharmacokinetic model for Efmody, which indicated similar pharmacokinetics in the two populations. Clinical opinion stated that data identified in the literature for adults with CAH would also be applicable for adolescents.
Cardiovascular events	Patients under the age of 25 do not experience cardiovascular events.	The QRISK3 algorithm used to derive general population risks by age only reported results for people age 25 or older.[79] Given that the risk of a 25 year old experiencing an event is very small (<0.001% per month), it was assumed the risk for patients under 25 would be negligible.
Fractures	Osteoporotic fractures were assumed to occur at the same rate as non-vertebrae fractures and symptomatic vertebrae fractures were assumed to occur at the same rate as hip fractures.	Data specific to osteoporotic and symptomatic vertebrae fractures were not available in the literature. This assumption has been validated by clinical experts.
Obesity	The BMI of patients receiving Efmody is expected to reduce due to better control of cortisol and androgen levels. This is achieved in the model by patients treated with Efmody reducing their BMI to the same as general population over a 12-month period.	DIUR-006 study reported long-term data showing patients receiving Efmody maintained a steady weight. Clinical opinion stated that CAH patients receiving glucocorticoid replacement therapy have increased BMI compared to the general population and it would be expected that patients who have controlled cortisol due to Efmody are at a lower risk of obesity.
	The BMI multiplier of 1.23 reported for female CAH patients is also applicable to male patients	Based on clinical opinion that obesity is an issue for both male and female CAH patients
Fertility	All costs and utility decrements associated with conception are incurred when the age of patients in the model reaches the average age of parents 28.6 years (Danish values used for age).[132, 143]	A simplifying assumption for a sub-model due to the absence of more in-depth data relating conception to age.
	Utility decrement associated with infertility is assumed to apply for three years.	Conservative assumption due to lack of data
Height/Obesity	Height and obesity are modelled independently. Obesity is modelled using general population BMI data sourced from the literature. Multipliers are then applied to the data to generate expected BMI in each arm. If the height sub-model is active in the model and patients with Efmody are modelled to have height closer to that of the general population, their BMI is not affected and is still modelled from the same data.	The obesity model looks to explore the impact of weight control in the CAH population. Making the sub-model inter-dependent with height may overestimate the treatment effect of Efmody.
	No cost impact associated with obesity or reduced height	Aligns with assumption used in Alkindi submissions.
Height	Any reductions in height related to CAH are applied once the modelled period where growing occurs has ended.	The link between glucocorticoid exposure and final height reported in Pijnenburg-Kleizen et al.[63] is calculated using the mean mg/m^2/day over the duration of puberty. Applying the calculation each cycle would cause cyclical calculations as patients'

Category	Assumption	Justification
		height and thus BSA (m^2) fluctuates, causing inaccurate results.
Resource use	Resource use in the Efmody arm is reduced by 15%	The simplified Efmody treatment regimen is easy-to-remember and implement, and will lead to improved patient adherence; optimal disease control will also eliminate the need for time sensitive sampling, reducing the burden of disease monitoring and dose titration resulting in reduced healthcare resource use.
Sick day rules	Patients in the Efmody arm experience two sick day periods a year, while patients in the comparator arm experience three	Based on clinical opinion
Key: BMI, body mass index; BSA, body surface area; CAH, congenital adrenal hyperplasia		

8.6.2 Base case results

The base case results for Efmody versus glucocorticoid replacement therapy used in Denmark are presented in Table 60. The prices used in the model were based on AIP excl VAT.

Table 60: Model results

Technology	Costs (DKK)	LYs	QALYs	Incremental Costs (DKK)	Incremental LYs	Incremental QALYs	ICER (DKK/QALY)
Discounted results							
Standard care	1,020,428	22.45	16.72				
Efmody	1,292,522	24.75	20.29	272,094	2.29	3.57	76,276
Undiscounted results							
Standard care	3,194,389	50.46	36.32				
Efmody	3,681,192	59.05	47.53	486,803	8.58	11.20	43,447

Efmody is associated with an incremental gain of 3.57 QALYs per patient and is associated with an incremental cost of DKK 272 094. This results in an ICER of DKK 76 276 per QALY, highlighting that Efmody has the potential to be considered a cost-effective treatment for adolescent and adult patients with a life-threatening rare condition CAH in the Danish setting.

The model estimates that patients on the SOC arm will have an average of 6.5 adrenal crises during their lifetime and Efmody patient will have 3.3 adrenal crises during their lifetime (age of treatment initiation in the model = 12). Table 61 shows a breakdown of the discounted costs associated with treating CAH with Efmody or glucocorticoid replacement therapy. The cost of Efmody is the biggest driver of the incremental cost of treatment with Efmody compared to standard glucocorticoid therapy.

Table 61: Disaggregated costs, (discounted), DKK

	Efmody	SOC	Incremental
Drug acquisition costs	852,351	262,632	589,719
Monitoring costs	25,054	29,618	-4,564
Adrenal crisis costs	68,722	141,235	-72,512
CVD costs	41,958	81,456	-39,498
Fracture costs	33,986	70,586	-36,600
Fertility costs	5,995	14,098	-8,103
Diabetes costs	262,217	420,047	-157,831

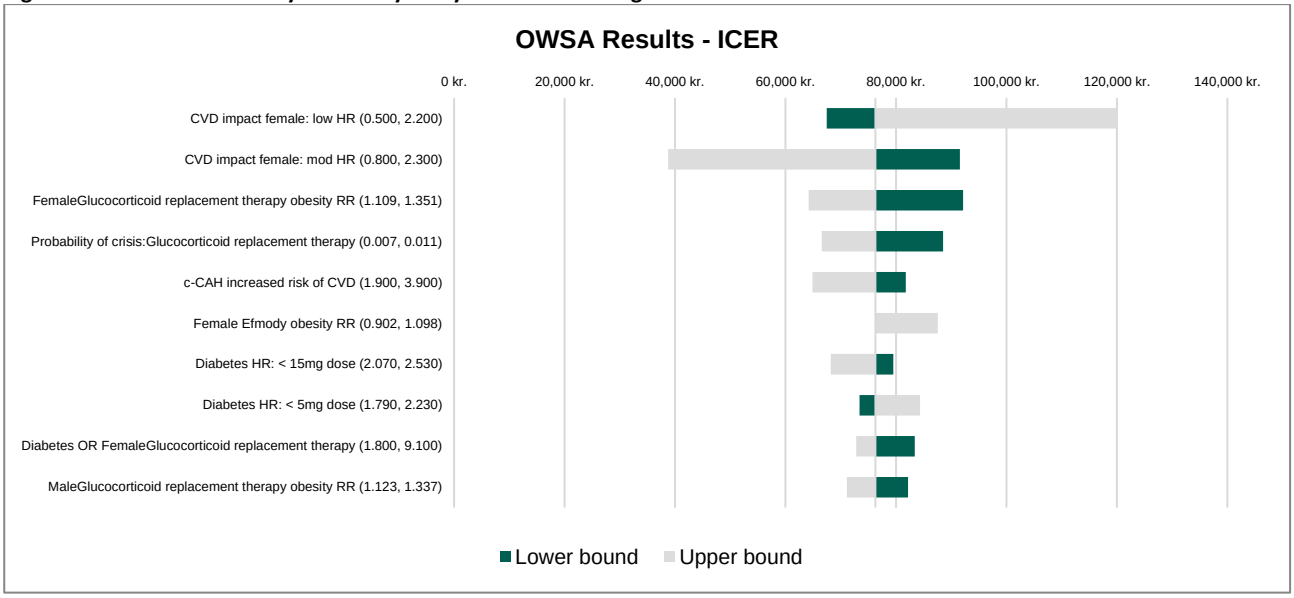
Although the model assumes that there are no differences in scheduled medical resource use and concomitant medication use between the treatment groups, small differences in these costs exist due to the improvement in survival attributed to Efmody.

8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

One-way sensitivity analysis explores the sensitivity in the base case model when one parameter is varied at a time. The top 10 influential parameters on the ICER are presented as a tornado diagram in Figure 15. As can be observed in this tornado diagram, the most influential parameters on the base case model results is the risk ratio of glucocorticoid replacement therapy on obesity and CVD impact in females. However, for all tested variability of parameters ICER is below DKK 120,000 per QALY.

Figure 15: Results of one-way sensitivity analysis – Tornado diagram



Key: GC, glucocorticoid; ICER, incremental cost-effectiveness ratio; OWSA, one way sensitivity analysis; QALY, quality adjusted life year; RR, relative risk

8.7.2 Probabilistic sensitivity analyses

Probabilistic sensitivity analysis (PSA) explores the sensitivity in the base case model when all model parameters are varied simultaneously, in order to capture the overall model uncertainty. The PSA was conducted by repeatedly sampling a random value for each parameter from its assigned distribution. The sampling was repeated with over 1,000 iterations and the total costs and QALYs in each iteration were recorded, these were used to calculate a mean probabilistic ICER.

The probabilistic base case model results show that Efmody generates an additional 3.18 QALYs at an incremental cost of DKK 266,775. The resulting ICER is DKK 83,857 per QALY as summarised in Table 62. The results show that the model outcomes are impacted by parameter uncertainty. However, when accounting for uncertainty in the model, the results still suggest Efmody has the potential to be cost-effective.

The probabilistic sensitivity analysis indicated that simultaneous variation in the parameter values resulted in Efmody having an incremental QALY gain versus glucocorticoid replacement therapy across all iterations.

Table 62: Probabilistic sensitivity analysis results (DKK)

Technology	Costs (DKK)	LYs	QALYs	Incremental Costs (DKK)	Incremental LYs	Incremental QALYs	ICER (DKK/QALY)
Standard care	1,231,235	22.43	16.66				

Efmody	1,498,011	24.52	19.84	266,775	2.09	3.18	83,857

*1000 times of probabilistic sensitivity analyses iteration. During the analysis every parameter is varied simultaneously on its given distribution, model outcomes are recorded and the process is repeated over a large number of iterations to calculate average model outcomes.

8.7.3 Scenario analysis

Extensive scenario analyses have been produced to test the uncertainty around modelling assumptions and to investigate the impact that this uncertainty has on the model outcomes. Table 63 describes each scenario and the original base case assumptions along with the ICER. The scenarios which have the greatest impact on the ICER are where patients only benefit from reduced exposure to glucocorticoid dosing in all sub models (332%), where patients only benefit from reduced exposure to glucocorticoid dosing in obesity sub model (80%), and where obesity sub model is excluded (66%).

These scenarios give valuable insight into which sub models are key drivers of model outcomes, given the clinical benefit demonstrated in DIUR-005 and DIUR-006, it is clinically implausible to assume that Efmody will only benefit patients by reducing their exposure to glucocorticoids. Furthermore, there is a wealth of evidence to support that patients with CAH have a higher BMI than the general population. All clinicians agreed that a link between glucocorticoid dosing and BMI exists and that the risk of obesity could be reduced if clinicians were able to control their patient's CAH without the use of excess glucocorticoids. Therefore, exclusion of this sub-model is not plausible.

Table 63: Scenario analyses

Scenario	Scenario ICER (DKK/QALY)	% change in ICER
1.5% discount rates	79,632	4%
No resource use reduction due to Efmody	77,955	2%
10% resource use reduction due to Efmody	76,814	1%
Zopf et al. informs glucocorticoid replacement therapy adrenal crisis rate (8.08/100 patient years)[49]	90,698	19%
Rushworth et al. informs adrenal crisis mortality (0.9%)77	99,662	31%
Falhammar et al. informs adrenal crisis mortality (3.9%)41	76,276	0%
Cardiovascular disease -Sub-model excluded	87,363	15%
Cardiovascular disease - Hormone control impact only	87,369	15%
Cardiovascular disease - GC dosing impact only	76,682	1%
Cardiovascular disease - Relative effectiveness vs Glucocorticoid replacement therapy. (50% effectiveness)	52,071	-32%
Obesity - Sub-model excluded	126,470	66%
Obesity - Hormone control impact only	76,191	0%
Obesity - GC dosing impact only	137,040	80%
Obesity - Only glucocorticoid replacement therapy BMI increase as glucocorticoid replacement therapy with females, reflective of CaHASE	88,160	16%
Obesity - Glucocorticoid replacement therapy BMI informed by Nguyen et al. (1.09)[92] for males and CaHASE for females (1.23)[10]	83,797	10%
Obesity - Glucocorticoid replacement therapy BMI informed by Nguyen et al. (1.09)[92]	106,705	40%
Obesity - Efmody BMI informed by Nguyen et al. (1.09)92	91,783	20%
Obesity - Utility from Sach et al.[107]	79,330	4%
Obesity - Utility from Macran et al.[108]	104,675	37%
Obesity - 24 months for Efmody patients to lose weight	76,276	0%
Obesity - 36 months for Efmody patients to lose weight	76,276	0%
Obesity - Include obesity related mortality	78,654	3%
Fractures - Sub-model excluded	89,201	17%
Fractures - Hormone control impact only	83,252	9%

Fractures - GC dosing impact only	87,449	15%
Fractures - Relative effectiveness vs Glucocorticoid replacement therapy. (50% effectiveness)	80,881	6%
Diabetes - Sub-model excluded	134,028	76%
Diabetes - Hormone control impact only	92,277	21%
Diabetes - GC dosing impact only	125,360	64%
Diabetes - Relative effectiveness vs Glucocorticoid replacement therapy. (50% effectiveness)	101,418	33%
Fertility - Sub-model excluded	78,603	3%
Fertility - 63% of patients conceive unassisted	77,253	1%
Fertility - 50% of patients conceive unassisted	77,597	2%
All models - Hormone control only	110,940	45%
All models - GC dosing impact only	329,230	332%
All models - Hormone control relative effectiveness to Glucocorticoid replacement therapy: 50% (Obesity modelled with Nguyen et al.92)	101,505	33%
All models - Hormone control only, relative effectiveness to Glucocorticoid replacement therapy: 50% (Obesity modelled with Nguyen et al.[92])	172,340	126%
Adolescents dose - 10 mg per day	67,509	-11%
Adolescents dose - 20 mg per day	85,117	12%
Growth - Sub-model excluded	79,004	4%
Growth - Hormone impact only	76,084	0%
Growth - GC dosing impact only	79,210	4%
Growth - Relative effectiveness vs Glucocorticoid replacement therapy. (50% effectiveness)	77,400	1%
85% of adult males receive Dexamethason 0.1 mg at night time	75,949	0%
6 years time horizon	278,949	266%
18 years time horizon	184,078	141%
Average hourly wage (179/hr) for an employee in Denmark after tax in the absence of better estimate	76,537	0.34%

8.7.4 Validation and generalisability

Once the model was finalised, it was validated by internal and external modellers. A programmer uninvolved in building the model reviewed all formulae and labelling in the model. Following this first validation step, an extreme value analysis was conducted. This involved inputting sensible upper and lower bounds (e.g. cost = 0, but not negative costs) into the model one parameter at a time and observing the corresponding changes in the results. Where it was not sensible to vary only one parameter or the expected effect on the results was not straightforward, a related group of parameters was varied simultaneously. The results were checked against their expected impact or the predicted direction of change for the varied parameter(s).

The cost-effectiveness model has undergone validation with multiple clinical experts to ensure the inputs and assumptions used in the model are appropriate. [12]

The model has also been validated with a health economics expert who agreed that the modelling approach used was appropriate to address the decision problem, with the available data.

9. Budget impact analysis

The current standard of care is cortisol replacement therapy and can be considered as a basket of different glucocorticoids. A simple budget impact model (BIM) is incorporated within the cost-effectiveness model to predict

the financial impact of providing Efmody to the healthcare system over a 5-year time period by considering the Efmody costs versus the costs of standard of care, the eligible patient population and market share estimates.
First, the size of the Danish CAH population was estimated. Danish population statistics for Efmody's license age, 12 years and older, were sourced from the Denmark Statistics. These values were multiplied by the incidence of CAH to estimate the eligible patient population Table 64. The average value from Norway and Sweden (Nermoen 2010, Lundberg 2017, Zetterström 2020) was used for estimation of incidence.
The cost of treating a patient with Efmody or SOC utilises cost-effectiveness model calculations noted in Section 8.5. while accounting for the annual cost of treatment acquisition, sick day medication, and healthcare resource use (CAH management) (Table 65). Different costs are associated with different sub-populations due to the variation in dose and the resource use required to manage CAH between adolescents, adults initially receiving Efmody who start at a higher dose, and adults receiving Efmody who have had their dose reduced to the optimal level.
The estimation of eligible CAH patients and predicted updated of Efmody in Denmark over the next five years is presented in Table 68. In 2026, Efmody is assumed to have a market share of 50% (n= 198 patients) of the total eligible patient population with CAH.
Efmody is assumed to mainly replace Plenadren (100%), prednisolone (100%) and a proportion of Hydrocortisone immediate-release for the treatment of adults with CAH. For the treatment of adolescents with CAH, Efmody is assumed to replace Alkindi (patients above the age of 12) and Hydrocortisone immediate-release tablets. As shown in Table 26, only a limited prescription of Alkindi is assumed for adolescents as it is mainly used for younger children and for adolescent who are having difficulties to swallow tablets.

Table 64: Budget impact - Eligible CAH patients and predicted uptake of Efmody in Denmark

	2022	2023	2024	2025	2026
Eligible patient population	364	364	365	366	368
Market share of Efmody	4%	10%	30%	40%	50%
Number of patients expected to receive Efmody	15	39	115	156	198

Notes: *Denmark statistics January 1, 2021, https://www.dst.dk/en, Denmark statistics: https://www.statbank.dk/statbank5a/selectvarval/define.asp?PLanguage=1&subword=tabsel&MainTable=FOLK1A&PXSId=199113, and assuming 0.4% annual population growth, https://www.worldometers.info/demographics/denmark-demographics/

The cost of treating a patient with Efmody or SOC utilises cost-effectiveness model calculations noted in Section 8 while accounting for the annual cost of treatment acquisition, sick day medication, and healthcare resource use (CAH management). Different costs are associated with different sub-populations due to the variation in dose and the resource use required to manage CAH between adolescents, adults initially receiving Efmody who start at a higher dose, and adults receiving Efmody who have had their dose reduced to the optimal level. Key non-drug acquisition related expenditure relevant for the the specialist health services with regards to CAH patients should be considered in the overall assessment and it is important to note that specialist health service cost estimates are likely to underestimate all costs occuring as part of specialised treatment CAH patients require given complexity of the disease and indivual treatment needs.

Table 65: Budget impact - costs per patient associated with Efmody and standard of care

	Efmody			Standard of care		
	Adolescents	**Adult - 1st year**	**Adult - subsequent year**	**Adolescent**	**Adult - 1st year**	**Adult - subsequent year**
Treatment costs, DKK	24,667	42,755	36,178	446	11,204	11,204
Sick day medication costs, DKK	35	35	35	22	552	552
Monitoring costs, DKK	3,174	652	652	4,003	821	821
Total, DKK	**27,876**	**43,442**	**36,865**	**4,470**	**12,577**	**12,577**

9.1 Budget impact results

Budget impact results considering both drug aqcuisition and other costs are presented in Table 66, Table 67, and Table 68. Overall budget impact in adolescent and adult CAH patients is low and predictable as CAH included in the newborn screening in Denmark - the overall budget impact is estimated to be 456, 955 in 2022, and 5,024,387 in 2026.

Table 66: Budget impact results - costs per patient associated with Efmody over time

	2022	2023	2024	2025	2026
Treatment costs, DKK	41,728	35,654	35,785	35,916	36,047
Sick day medication costs, DKK	35	35	35	35	35
Monitoring costs, DKK	795	766	738	709	680
Total, DKK	**42,558**	**36,456**	**36,558**	**36,660**	**36,762**

Table 67: Budget impact results - costs associated with SOC over time

	2022	2023	2024	2025	2026
Treatment costs, DKK	10,593	10,715	10,837	10,960	11,082
Sick day medication costs, DKK	522	528	534	540	546
Monitoring costs, DKK	1,002	966	930	893	857
Total, DKK	**12,117**	**12,209**	**12,301**	**12,393**	**12,485**

Table 68: Budget impact results - annual and cumulative budget impact results for Efmody vs SOC

	2022	2023	2024	2025	2026
Annual budget impact in year, DKK					
Efmody	638,368	1,568,229	4,657,715	5,942,830	7,491,831
SOC	181,753	472,557	1,393,438	1,890,230	2,472,102
Efmody - SOC	**456,955**	**1,096,555**	**3,266,881**	**4,056,133**	**5,024,387**
Cumulative budget impact, DKK					
Efmody	638,368	2,206,597	6,864,313	12,807,143	20,298,974
SOC	181,413	653,087	2,043,922	3,930,619	6,398,063
Efmody - SOC	**456,955**	**1,553,510**	**4,820,391**	**8,876,524**	**13,900,911**

10. Discussion on the submitted documentation

10.1 Direct and indirect evidence of clinical efficacy

DIUR-005 is the first randomised controlled trial of glucocorticoid replacement therapy for patients with CAH. In the trial, patients who received Efmody had superior hormonal control during the morning and early afternoon compared to those receiving standard glucocorticoid therapy.[16] Standard glucocorticoid therapy (comprising hydrocortisone only, prednisone or prednisolone alone or in combination with hydrocortisone, and dexamethasone alone or in combination with any other glucocorticoid) was chosen as the comparator arm as it represents the best care possible with current available therapies, including those used in Denmark.[12, 15]

As DIUR-005 is the largest interventional study in CAH to date, and the lack of earlier published clinical trial experience for CAH outside of Efmody, meant that no insights could be gained from any competitor studies to inform the choice of endpoints in DIUR-005. Thus, protocol assistance was sought from the EMA (EMA/CHMP/SAWP/430444/2014). The primary endpoint, change from baseline to 24 weeks of the mean of the 24-hour SDS profile for 17-OHP (which was based on the DIUR-003 Phase II trial[20]), was proposed by Diurnal as a way of measuring effects of over-treatment and under-treatment. This endpoint was accepted by the CHMP with caveats that it may not be good at assessing changes in amplitude (i.e. the variability of 17-OHP throughout the day) and that values within the normal range for 17-OHP may impact the analysis. In view of these concerns, the CHMP stated that raw data analysis of the change from baseline in the 24-hour profile would be informative, as would a measure looking specifically at amplitude changes in 17-OHP.

The DIUR-005 study failed to meet its primary endpoint of superiority in change from baseline to 24 weeks of the mean of the 24-hour SDS profile for 17-OHP because the SDS analyses missed the morning improvement in biochemical control on Efmody. Several aspects of the trial design are likely to have contributed to the loss of statistical significance between groups. A limitation of the pre-defined SDS analysis of the PEM was that it included an unsigned SDS score (i.e. both directions of deviations from the reference range included to account for both under- and over-treatments, but the analysis did not differentiate between high and low 17-OHP values) over the 24-hour period. Upon inspection of the geometric mean 24-hour profiles it was apparent that this endpoint was impacted by fluctuations in hormonal levels based on the natural daily circadian rhythms. On average over a 24-hour period, these cancelled each other out and this may explain the lack of evidence of a treatment effect, which was clearly seen on the graphs of the change in 24-hour profile from baseline, as predicted by CHMP. Overall, the SDS analysis overemphasised scores below the midpoint of the reference range and the logarithmic transformation and use of a mean score over 24 hours obscured the impact of Efmody in the morning and early afternoon. The intense titration protocol utilised in DIUR-005 (that is, the use of 24-hour overnight androgen profiling, blinded titrators and hospital visits at 0, 1, 3 and 6 months) may also have limited the ability to show a treatment effect. However, it should be noted that such a monitoring and titration scheme is not likely to be practical, affordable or desirable in a normal clinical setting, a lesson taken forward into DIUR-006 where a more real-world style monitoring was utilised (and which demonstrated disease control with Efmody on a meaningfully lower dose).

In retrospect, the SDS analysis was not the best measure to use as the primary outcome. Following a review of these pre-defined analyses results, the previous EMA scientific advice was revisited and a number of *post hoc* analyses of the primary endpoint were conducted in line with the EMA scientific advice, and these provided evidence of improved control of 17-OHP and a consistent benefit over standard glucocorticoid therapy with Efmody. This indicated that the use of SDS analysis as the primary endpoint was not suited to analyses of biomarkers with inherent diurnal variations. In addition, while no correction for multiple *post hoc* analyses was performed, it was considered that these *post hoc* analyses were robust due to the prospective specification of these analyses by the EMA scientific advice, the variety and extensiveness of the efficacy analyses, their scientific plausibility, and the consistency with which they favour Efmody, despite evidence that, by chance, the Efmody group was less in control at baseline. Overall, the potential issues flagged by the CHMP at Protocol Assistance were seen at 24 weeks in the study, and when the data were analysed in the way the CHMP suggested as an adjunct to the primary analysis the study clearly demonstrated improved control in the Efmody cohort. Indirect comparison with the largest available published cohort studies (US and UK[8, 10]) showed that the disease control data in the Efmody Phase III study (DIUR-005) were comparable with 'real world' data at baseline, but Efmody patients had considerably improved control after 6 months therapy. This control was maintained in the DIUR-006 extension study at a lower dose than that reported in the literature for standard

glucocorticoid therapy. Over the course of the DIUR-006 extension study, a reduction in the Efmody median total daily dose of [redacted] was observed, which represents a clinically meaningful steroid sparing effect.[34]
Taken together, the clinical data for Efmody indicates that while the analysis of the PEM defined for the primary outcome suppressed statistical differences between the two groups, evaluation of the trial data as a whole, and in the context of published literature, demonstrates that Efmody is able to normalise cortisol and androgen levels in CAH, particularly in the early morning, and brings androgen levels in line with that reported in healthy individuals.[32, 33] This means that for patients with CAH, the disease control that Efmody provides will led to a better balance between control of excess androgen and the dose of steroid required throughout their life, leading to long-term health benefits. Indeed, this was observed in both DIUR-005 and DIUR-006 where, compared to the standard glucocorticoid therapy group, patients receiving Efmody had a reduced risk of adrenal crises, reduced usage of sick day rules, weight stabilisation, preservation of bone density and metabolic health (CAH patient cohort at baseline of DIUR-005 had bone and metabolic health markers within normal range).[16] Furthermore, the benefits of Efmody included the improved fertility outcomes as evidenced by restoration of menstruation, pregnancies and partner pregnancies for women and men with CAH on Efmody.
It should also be noted that the open-label nature of DIUR-005 and DIUR-006 may have introduced bias, as the patients and investigators were not blinded to the treatment allocation. However, bias was minimised in DIUR-005 through the use of independent blinded physicians who made the dose adjustment decisions. The relatively short study duration of DIUR-005 was also a limitation, as long-term clinical benefits of biochemical disease control (such as on bone health, CVD risk and weight), or significant differences in quality of life measures, were not given sufficient time to be observed. However, data from the ongoing DIUR-006 extension study provides additional evidence on the long-term clinical and safety of Efmody. Of note, while baseline characteristics across treatment cohorts in DIUR-005 were balanced with regards to patient demographics, it was observed that at baseline, the number of patients with good baseline disease control was higher in the standard glucocorticoid therapy group than in the Efmody group (61.5% vs 37.7%). Randomisation was conducted using an Interactive Web Response System (IWRS), with stratification being based on patient's current treatment at the time of entering the study, and so this imbalance was a chance finding. Analyses revealed that the imbalance in baseline response between the two treatment groups did not over-emphasise the week 24 differences between the groups, but in fact, adjustment for baseline response strengthened the differences between the two groups. In addition, despite the observed differences at baseline, it is notable that when patients entered the long-term DIUR-006 extension study, patients treated with standard glucocorticoid therapy achieved disease control with Efmody. The close approximation of physiological levels of cortisol with Efmody are shown to benefit patients with CAH, irrespective of prior treatment.
Due to lack of published comparative data on currently used glucococorticoids in CAH patients it was not possible to conduct formal indirect comparisons. However, based on naive indirect comparison to literature values, Efmody offers better disease control with lower steroid dose compared to current standard glucocorticoids while the safety profile of Efmody does not differ from that of immediate-release hydrocortisone.

10.2 Economic evidence

It is challenging to generate robust economic evidence for a rare and complex disease requiring lifelong daily treatment, such as CAH. That is why both Efmody cost-effectiveness model approach and inputs were validated by several clinical and health economics experts to ensure model is plausible and reflects clinical reality appropriately. In addition, comprehensive sensitivity and scenario analyses were conducted to ensure robustness of the model.
Based on the health effect and utility analysis looking into the impact of physiological cortisol replacement, androgen control and clinically meaningful steroid dose reduction achieved with Efmody to key outcomes in CAH patients (as agreed with seven clinical experts), Efmody results in incremental gain of 2.29 LYs and 3.57 QALYs. These results are likely to underestimate benefits of Efmody given the complexity of CAH disease is and wide-ranging potential benefits of physiological cortisol replacement particularly when started at the age of 12 years when development is still ongoing.

10.3 Conclusion

Efmody is the first modified-release hydrocortisone for CAH and is proven to mimic the physiological profile of cortisol day and night. Compared with patients who received glucocorticoid replacement therapy, patients receiving Efmody had normalised androgen levels in the crucial early morning period and throughout the day. This improvement of androgen control in the morning with Efmody is aligned with its mode of action of producing a normalised 17-OHP profile.

Data from the long-term Phase III DIUR-006 extension study demonstrated sustained biochemical control with Efmody at a physiological dose (median total daily dose of 30mg at baseline was reduced to a median [redacted] over ~12 months). Glucocorticoid dose is associated with increased risk of comorbidities. Clinical experts noted that a reduction in dose of 5mg or more would be clinically meaningful and result in clinical changes for patients.[34]

The normalisation of cortisol and androgen level and the reduced dose of glucocorticoids should lead to long-term benefits for patients – including reduction of the risk of adrenal crisis, cardiovascular disease, fractures, diabetes and obesity, and improved fertility and final height. This results in cost savings, improved HRQL outcomes and reduced mortality.

When treatment is initiated at 12 years old, Efmody is associated with an incremental gain of 3.57 QALYs per patient and an ICER of DKK 76,276 per QALY. The analysis also highlights that the results are robust to changes in a number of key parameters and scenarios.

Further to this, Efmody has a simple and easy-to-remember twice-daily treatment regimen, which is anticipated to increase patient compliance and provide an easy-to-deliver and is anticipated to reduce the burden of disease monitoring and dose titration resulting in reduced healthcare resource use and cost savings. The model estimates costs savings in relation to reduced resource use of over a patient's lifetime and cost savings as a result of reduced hospitalisations due to CAH patients receiving Efmody experiencing fewer adrenal crises. Results show that further savings may arise from reduced fertility interventions, reduced cardiometabolic burden (cardiovascular disease and diabetes) and reduced bone fractures, leading to reduced resource use.

In conclusion, these results indicate that Efmody is a cost-effective treatment. The assumptions made in the model are conservative whenever possible, which potentially results in the underestimation of the benefits of Efmody. The overall budget impact is estimated to be DKK 5,024,387 in year 5 from launch.

11. List of experts

No official interviews with Danish clinical experts were conducted as part of the Efmody DMC reimbursement application preparation process. However, information from previous market research projects regarding Efmody and/or new treatments for adolescents and adults with CAH, or paediatric AI (as part of Alkindi commercialisation projects), which included (anonymous) Danish clinical experts, was utlised. It is not possible for Diurnal to disclose names of clinical experts who took part in market reseach to maintain agreed confidentiality and anonymity.

Feedback regarding the current treatment landscape was received from the Danish Efmody clinical triallist, Professor Anders Juul.

To gain clinical validation on the literature identified from evidence generation activities to support the model structure and the data inputs for the cost-effectiveness model the set of interviews were conducted with seven key European clinical experts including. Swedish Professor Anna Nordenström), and Associate Professor Henrik Falhammar from Sweden, and Associate Professor Ingrid Nermoen from Norway

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149. TLV Alkindi assessment report: https://www.tlv.se/download/18.2eb4319b1668af6a7cdd05f1/1540556038981/bes181025_alkindi.pdf
150. Plenadren SmPC: https://www.ema.europa.eu/en/documents/product-information/plenadren-epar-product-information_en.pdf
151. Prednisolone SmPC: https://pro.medicin.dk/Medicin/Praeparater/56#
152. Dexamethasone SmPC: https://pro.medicin.dk/Medicin/Praeparater/7255
153. Alkindi SmPC: https://www.ema.europa.eu/en/documents/product-information/alkindi-epar-product-information_da.pdf

Appendix A – Literature search for efficacy and safety of intervention and comparator(s)

Clinical and economic SLRs did not identify any additional relevant studies (to Efmody pivoral Phase III trial DIUR-005, which is presented in Section 7) on efficacy and safety of Efmody and comparator. Therefore, SLR reports are provided as embedded documents below rather than full details provided in Appendix A.

File	Embedded Link
Clinical SLR	2846_Diurnal Chronocort_Clinical
Economic SLR	2846_Diurnal Chronocort_Econon

Appendix B Main characteristics of included studies

Table 69: Efmody clinical trial programme – list of all clinical studies

Study reference/ID/study name	Conflicts of interest	Study location or regions	Source of identification	Available documentation	Dates of study (start and [expected] completion date); status (ongoing/ complete)	Study used in economic evaluation (Yes/No?)
Randomised controlled trials						
DIUR-002; NCT03051893	Sponsored by Diurnal	UK	ClinicalTrials.gov	Clinical Trials.gov	Completed (study completion date: April 2012)	No
DIUR-004; NCT02408068	Sponsored by Diurnal	UK	ClinicalTrials.gov	Clinical Trials.gov	Completed (study completion date: March 2015)	No
DIUR-005; NCT02716818	Sponsored by Diurnal	Global (7 countries)	ClinicalTrials.gov	Clinical study report; Clinical Trials.gov	Completed (study completion date: July 2018)	Yes
DIUR-008; NCT03343327	Sponsored by Diurnal	UK	ClinicalTrials.gov	Clinical Trials.gov	Completed (study completion date: April 2018)	No
Non-randomised studies						
DIUR-003; NCT01735617	Sponsored by Diurnal	US	ClinicalTrials.gov	Mallappa et al. 2014[17]; Clinical study report; Clinical Trials.gov	Completed (study completion date: December 2013)	No
DIUR-006; NCT03062280	Sponsored by Diurnal	Global (5 countries)	ClinicalTrials.gov	Study Protocol; Clinical Trials.gov	Study start date: August 2016. Estimated completion date: February 2022 (Final data collection date for primary outcome measure)	Yes

Note: The trials NCT00519818 (conducted in the US – PK study of Cortef® vs Efmody® in CAH) and DIUR-007 (NCT03532022; suspended) which are listed on clinicaltrials.gov are absent from this overview table as they are not included in the Clinical Overview document.
Source: ClinicalTrials.gov.

Table 71: Methods of data collection and analysis of outcomes in pivotal trial DIUR-005 and extension study DIUR-006

<table>
<tr><th>Study reference/ID</th><th>Endpoint definition</th><th>Method of data collection</th><th>Method of analysis</th></tr>
<tr><td>DIUR-005; NCT02716818</td><td>Primary efficacy endpoint: The change from baseline to 24 weeks of the mean of the 24-hour SDS profile for 17-OHP. The SDS profile was calculated as the SDS of log-transformed 17-OHP concentration unsigned.</td><td>For the baseline assessment, patients were admitted overnight for a 24-hour endocrine profile whilst remaining on their standard GC therapy, with 17-OHP and A4 blood 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.</td><td>Statistical analysis
Null (H0) hypothesis: there was no difference between the mean change from baseline to 24 weeks in the primary efficacy variable (the natural logarithm of the mean of the 24-hour SDS profile for 17-OHP) in Efmody compared with standard GC therapy.
Note: the difference analysed was the mean of the primary efficacy analysis variable for Efmody minus the mean of the primary efficacy analysis variable for standard GC therapy; this means that a negative difference favours Efmody.
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 below). The SDS gave equal weight to over suppression and under suppression.
Table: Reference range for 17-OHP and A4 in DIUR-005
<table>
<tr><th>Marker</th><th>Male</th><th>Female</th></tr>
<tr><td>17-OHP</td><td>1.2*–6.7 nmol/L</td><td>1.2*–8.6 nmol/L</td></tr>
<tr><td>A4</td><td>1.4–5.2 nmol/L</td><td>1.0–7.0 nmol/L</td></tr>
<tr><td colspan="3">Note: the upper range for females is during the luteal phase.
Key: *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.
Source: Mayo Clinic. http://www.mayomedicallaboratories.com/test-catalog</td></tr>
</table>
The comparison between treatment groups was performed using anormal analysis of covariance (ANCOVA) linear model, with the unadjusted mean of the primary efficacy variable being presented, along with the least squares (LS) estimated mean.
Lower values reflected a reduction in the variability of 17-OHP over the 24-hour period, hence negative changes versus baseline indicated better hormonal control. The primary efficacy endpoint was compared with treatment groups using ANCOVA linear model with pre-baseline standard therapy and the primary efficacy variable at baseline as covariates. The unadjusted mean of the primary efficacy variable was presented along with</td></tr>
</table>

Study reference/ID	Endpoint definition	Method of data collection	Method of analysis
			the least squares (LS) estimated mean. The difference in LS means (Efmody group minus standard GC therapy group) was presented with the associated 95% 2-sided CI and 2-sided p-value. There was no adjustment for multiple testing as the primary analysis was considered the main analysis with the secondary and exploratory endpoints intended as support for the primary analysis. **Handling of withdrawals, discontinuations and missing data** 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 time point (including out-of-window measurements). If 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. Analyses performed in the FAS used a last-one carried forward approach for patients who discontinued early from the study; in addition, a rule for imputing completely missing endocrine results at the 15:00 planned time points within a 24-hour profile was added. When calculations had to be based upon incomplete dates, the following process was used. If year was missing, no imputing was conducted, and the value was considered missing. If year was populated but both month and day were missing, then the date defaulted to 1 July. If day only was missing, then the day defaulted to Day 15 of the month.
	<u>Secondary endpoints</u>		
	The 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)	Baseline blood samples were taken for safety assessments and the evaluation of other endpoints on the second morning.	**Statistical analysis** The primary analysis was repeated for A4; that is, change from baseline to 24 weeks of the logarithm of the mean of the 24-hour SDS profile for A4, the same hypothesis as the primary analysis was tested, with A4 in place of 17-OHP. **Handling of withdrawals, discontinuations and missing data** See primary endpoint row above.
	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)		**Statistical analysis** The natural logarithm of the means over the partial profiles of 17-OHP and A4 at 15:00–23:00 hours, 23:00–07:00 hours, and 07:00–15:00 hours (all refer to actual clock time of sampling) for Week 24 were calculated, with the first and last observations weighted half compared with the others. **Handling of withdrawals, discontinuations and missing data** See primary endpoint row above.

Study reference/ID	Endpoint definition	Method of data collection	Method of 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)		**Statistical analysis** A responder analysis was conducted to compare the response between the Efmody group and the standard GC therapy group (EES) using logistic regression with adjustment for pre-baseline therapy strata. The responder analysis tested the null hypothesis H01: the odds of response for Efmody was the same as the odds of response for standard GC therapy i.e. the odds ratio was 1, versus the alternative hypothesis H11: the odds of response for Efmody was different to the odds of response for standard GC therapy. An odds ratio of greater than 1 favours Efmody. The hypothesis was tested separately for 17-OHP and A4. A patient was considered a responder if their 09:00 hour result at Week 24 was in the optimal.[1] **Handling of withdrawals, discontinuations and missing data** See primary endpoint row above.
	Changes relative to standard GC therapy in body composition (DEXA) (fat mass, lean mass and total bone density) - measured at all sites except Germany		**Statistical analysis** For the secondary endpoint of the change from baseline in body composition (DEXA), the results from the three tests: fat mass, lean mass, and total bone density were analysed separately using an ANCOVA linear model. The results from each test were used in turn to test the null hypothesis H02: There was no difference between the mean change from baseline to 24 weeks in the result for Efmody compared with standard GC therapy, versus the alternative hypothesis H12: There was a difference in the mean change from baseline to 24 weeks in the result for Efmody compared with standard GC therapy. Summary statistics were produced for the absolute values and change from baseline in body composition (DEXA) at each visit (Weeks 4, 12 and 24). **Handling of withdrawals, discontinuations and missing data** See primary endpoint row above.
	<u>Exploratory endpoints</u>		
	Partial AUC of 17-OHP at 15:00–23:00, 23:00–07:00 and 07:00–15:00		**Statistical analysis** The natural logarithm of the means over the partial profiles of 17-OHP and A4 at 15:00–23:00 hours, 23:00–07:00 hours and 07:00–15:00 hours (all refer to actual clock time of sampling) for Week 24 were calculated, with the first and last observations weighted half compared with the others. **Handling of withdrawals, discontinuations and missing data** See primary endpoint row above.

Study reference/ID	Endpoint definition	Method of data collection	Method of analysis
	The primary endpoint measure presented for the profiles measured at 4 and 12 weeks for the purposes of titration		**Statistical analysis** For efficacy analyses based on the Week 12 and Week 24 visits, patients who had withdrawn from the study were assessed based on the latest available 24-hour profile. **Handling of withdrawals, discontinuations and missing data** See primary endpoint row above.
	Changes relative to standard GC therapy in the following: Bone markers - serum CTX and osteocalcin (after fasting) hsCRP Assessment of glucose and insulin in the morning (after fasting) Assessment of HbA1c, total testosterone, and PRA in the morning QoL using SF-36, MAF, and EQ-5D		**Statistical analysis** Change from baseline was calculated at each visit (Week 4, Week 12 and Week 24) and summary statistics presented for both absolute values and change from baseline by treatment group, pre-baseline therapy strata and visit. Shift tables of baseline to minimum and maximum on-treatment were produced for the appropriate parameters, displaying the number and percentage of patients in each of the categories (High, Low and Normal) relative to the category of their baseline assessment. Boxplots of change from baseline over time for each bone marker or laboratory assessment of special interest were produced. Changes relative to standard GC therapy in QoL at 24 weeks were measured using the three instruments of SF-36, MAF, and EQ-5D. The change from baseline and percentage change from baseline at Week 24 were calculated, with summary statistics for absolute values at each visit, and change and percentage change from baseline at Week 24 being tabulated by treatment group and pre-baseline therapy strata. **Handling of withdrawals, discontinuations and missing data** See primary endpoint row above.
	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		**Statistical analysis** Use of GCs at Visit 1 (baseline) and Visit 4 (Week 24) of the study were presented as individual GCs used. Changes in dose of last GC from baseline to each visit were presented as hydrocortisone equivalents using the Finkielstain conversion factors (prednisone/prednisolone dose was multiplied by 5, and dexamethasone dose was multiplied by 80). Additional exploratory and sensitivity analyses could have been included if necessary following discussion at the Data Review Meeting. **Handling of withdrawals, discontinuations and missing data** See primary endpoint row above.
	Safety: Included vital signs and routine haematology and biochemistry; clinical AEs (particularly use of sick day rules and		**Statistical analysis**

Study reference/ID	Endpoint definition	Method of data collection	Method of analysis
	Addisonian crises. Note: under- or over-replacement with GCs were considered in the efficacy endpoints); and changes relative to standard GC therapy in weight, BMI, waist circumference, and BP		AEs were coded using MedDRA Version 20.0. Only AEs reported up to the follow-up telephone call after the Week 24 visit were summarised. Where severity was displayed, if a patient had more than one AE of the same term, the maximum severity was used. All AEs that led to use of sick day rules, adrenal crises, and AEs of unexpected therapeutic benefit were summarised. Changes from baseline in laboratory parameters and vital signs were calculated at each visit (Week 4, Week 12 and Week 24) and summary statistics presented for both absolute values and change from baseline by treatment group, pre-baseline therapy strata and visit. **Handling of withdrawals, discontinuations and missing data** For AEs and concomitant medications, if the year was missing no imputing was conducted. If start year was populated but both the month and day were missing, or if the month was missing and day was present, then the date defaulted to 1 January. If the day only was missing, then the day defaulted to Day 1 of the month. If the end year was populated but both month and day were missing, or if the month was missing and day was present, then the date defaulted to 31 December. If the day only was missing, then the day defaulted to last day of the month. For the definition of treatment-emergent and ongoing, if only partial dates were available for the start and end, then a conservative approach was taken, and the event was assumed to be treatment-emergent/ongoing.
	<u>*Post-hoc* analyses</u>		
	Following a review of the pre-defined analyses results, the previous EMA scientific advice was revisited and a number of *post-hoc* analyses advised in the 2014 protocol assistance procedure (procedure EMEA/H/SA/856/3/2014/PA/III) 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 and a 1-sided SDS score for low values using only the upper boundary of the reference range. Additional analyses were also conducted using the unsigned SDS score from the upper limit of the reference range and the unsigned SDS score from the lower limit of the reference range. A *post-hoc* analysis was also conducted on responders but using the reference range for 17-OHP rather than the optimal range used in the pre-defined secondary endpoint. Further *post-hoc* analyses were also conducted on the daily dose of steroids used in the Efmody and standard GC therapy groups and the analysis of dose titrations recommended by the independent blinded physicians was repeated by the hydrocortisone only subgroup. A *post-hoc* analysis was also conducted on the log-transformed AUCs for 17-OHP and A4. A *post-hoc* analysis was also conducted on the median total daily dose by BSA using the hydrocortisone dose equivalent. For this analysis, BSA (m^2) was calculated using the Dubois formula [weight (kg)$^{0.425}$] x [height (cm)$^{0.725}$)] x 0.007184.		

Study reference/ID	Endpoint definition	Method of data collection	Method of analysis
DIUR-006; NCT03062280	Primary endpoint: Safety The primary endpoint was the safety of Efmody over time, assessed using (but not limited to) the following endpoints: Signs and symptoms of AI or over-treatment Use of sick day rules Occurrence of adrenal crises Occurrence of AEs Change from pre-Efmody baseline in safety laboratory assessments at each visit Change from pre-Efmody baseline in vital signs, weight, BMI, and waist circumference at each visit	Blood samples (maximum of 49mls) were taken for the following: Routine safety laboratory tests Measurement of serum CTX, osteocalcin, hsCRP, HbA1c, testosterone, fasting insulin and glucose. The fasting samples were taken as soon as possible after the patient arrived for the visit before any food was consumed Measurement of PRA after the patient had been supine for 30 minutes Testing of 17-OHP and A4 levels (samples were taken at 09:00 and 13:00 hours; baseline, Week 4, Week 12, Week 24 and a 6-montly visit) Genotyping, if necessary, from patients who entered from Study DIUR-003, unless genotyping had previously been performed, in which case the patient was asked for their permission for this information to be taken from their medical records	**Statistical analysis** AEs were coded using MedDRA Version 20.0. Only AEs up to 30 days after the end of the study or the early withdrawal visit were included in summary tables. All AEs that led to use of sick day rules, adrenal crises, and AEs of unexpected therapeutic benefit were summarised. Changes from pre-Efmody baseline in vital signs data, weight, BMI, and waist circumference were summarised over time, with boxplots of change from pre-Efmody baseline presented over time. Signs and symptoms of AI and over-treatment were summarised over time by feeder study and previous treatment. **Handling of withdrawals, discontinuations and missing data** For AEs and concomitant medication, the imputation rules were based on the date of Efmody administration. For patients who were still on treatment at the time of the interim analysis, the data-cut off was used as the date of last dose in the calculation of exposure.

Study reference/ID	Endpoint definition	Method of data collection	Method of analysis
	Secondary endpoints (efficacy)		
	Disease control as assessed by both 17-OHP and A4 levels in the optimal and reference range, respectively, at 09:00 and at 13:00	See data collection method for primary endpoint	**Statistical analysis** Although data were collected for efficacy analysis, no statistical inference testing was planned or performed. Disease control was based on whether 17-OHP levels were in the optimal range and whether the A4 levels were in the reference range (both analysed separately). A patient was considered a responder (i.e. disease controlled) if their 09:00 results were in the optimal range for 17-OHP and then separately if their 09:00 results for A4 were in the reference range. The number and percentage of patients who achieved results in the optimal range were presented at each visit. This was repeated for the 13:00 values. **Handling of withdrawals, discontinuations and missing data** Missing 17-OHP and A4 values (including those considered missing due to being taken outside the permitted time window) were not imputed. In calculating the mean of the 09:00 and 13:00 SDS, if one value was missing, then only the non-missing value was used. If both values were missing, the mean value was missing. When calculations were based upon incomplete dates, the following process was used. If year was missing imputation was not done; the value was considered missing. If year was populated but both month and day were missing, the date defaulted to 1 July. If day only was missing, the day defaulted to Day 15 of the month.
	Change from pre-Efmody baseline at each visit in unsigned SDS of 17-OHP and A4 at 09:00, 13:00 and the mean of the two time points. Pre-Efmody baseline means prior to the first dose of continuous Efmody which is: The reassessed baseline under DIUR-006 for patients entering from Study DIUR-003 and those patients from DIUR-005 who had a gap between completing Study DIUR-005 and starting Study DIUR-006 Visit 4 (Week 24) from the feeder study for patients who received standard GC replacement therapy in Study DIUR-005 and immediately entered DIUR-006 Prior to the first Efmody dose in Study DIUR-005 for patients who received		**Statistical analysis** The SDS was defined as the absolute (unsigned) number of SDs above or below the average of the lower and upper limit of normal. The reference ranges used for this analysis were as follows: 17-OHP: 1.2 to 6.7 nmol/L in males; 1.2 to 8.6 nmol/L in females A4: 1.4 to 5.2 nmol/L in males; 1.0 to 7.0 nmol/L in females For each of the 17-OHP and A4 concentrations at each visit at each time point (09:00, 13:00), the natural logarithm was taken and the SDS was calculated by counting the number of SDs above or below the mean of the log-transformed range. The mean of the SDS scores for each androgen was calculated over the two time points (see DIUR-006 CSR). The mean of the 'normal' log-transformed range was calculated by taking the natural logarithm of the upper and lower limit, calculating the range of the log-transformed values, and finding the midpoint of the range. The SD of the log-transformed range was approximated by dividing the range of the log-transformed values by 4. **Handling of withdrawals, discontinuations and missing data**

Study reference/ID	Endpoint definition	Method of data collection	Method of analysis
	Efmody in Study DIUR-005 (i.e. DIUR-005 baseline visit) and immediately entered DIUR-006		Missing 17-OHP and A4 values (including those considered missing due to being taken outside the permitted time window) were not imputed. In calculating the mean of the 09:00 and 13:00 SDS, if one value was missing, then only the non-missing value was used. If both values were missing, the mean value was missing. When calculations were based upon incomplete dates, the following process was used. If year was missing imputation was not done; the value was considered missing. If year was populated but both month and day were missing, the date defaulted to 1 July. If day only was missing, the day defaulted to Day 15 of the month.
	Change from pre-Efmody baseline at each visit in the absolute values of 17-OHP and A4 at 09:00 and 13:00		**Statistical analysis** The geometric mean of the 17-OHP measurements at 09:00 over time (by visit) were plotted along with the 95% CIs for the overall DIUR-006 study. This plot was repeated by feeder study and previous treatment. These plots were repeated for 17-OHP measurements at 13:00 and A4 measurements at 09:00 and 13:00. Individual participant profile plots were also produced displaying 17-OHP measurements at 09:00 over time (on a logarithmic scale). These profile plots were repeated for 17-OHP measurements at 13:00 and A4 measurements at 09:00 and 13:00.. **Handling of withdrawals, discontinuations and missing data** Missing 17-OHP and A4 values (including those considered missing due to being taken outside the permitted time window) were not imputed. In calculating the mean of the 09:00 and 13:00 SDS, if one value was missing, then only the non-missing value was used. If both values were missing, the mean value was missing. When calculations were based upon incomplete dates, the following process was used. If year was missing imputation was not done; the value was considered missing. If year was populated but both month and day were missing, the date defaulted to 1 July. If day only was missing, the day defaulted to Day 15 of the month.
	Change from pre-Efmody baseline at each visit in: Bone turnover markers - CTX, osteocalcin Testosterone (total) Fasting insulin and blood glucose levels, and HbA1c hsCRP and PRA Body composition (DEXA) (fat mass, lean mass and total bone density) (except in Germany)		**Statistical analysis** Change from pre-Efmody baseline in bone turnover markers, testosterone, fasting insulin, blood glucose levels, HbA1c, hsCRP, PRA, DEXA, QoL questionnaires were all summarised over time. DEXA scans were performed at baseline for patients who entered from Study DIUR-003, then annually for all patients. DEXA scans were not performed in Germany due to objections to this procedure by the Regulatory Authority. Patients who had a gap between completing Study DIUR-005 and starting Study DIUR-006 did not require an additional DEXA scan at the time they entered Study DIUR-006. The DEXA scans were performed according to the site's standard clinical procedures.

Study reference/ID	Endpoint definition	Method of data collection	Method of analysis
	QoL – SF-36, MAF, EQ-5D		The QoL questionnaires used (MAF, SF-36 and EQ-5D) were all validated QoL scales and were administered and completed in a quiet environment. **Handling of withdrawals, discontinuations and missing data** See secondary efficacy endpoints.
	Total daily dose of Efmody in mg/day of hydrocortisone and incidence of dose titrations		**Statistical analysis** The total daily dose of Efmody in mg/day of hydrocortisone was summarised over time. Exposure to Efmody (time since first dose), the incidence of dose titrations by visit, and the reasons for dose increases or dose decreases over the course of the study were also summarised. **Handling of withdrawals, discontinuations and missing data** See secondary efficacy endpoints.

Key: 17-OHP, 17-hydroxyprogesterone; A4, Androstenedione; AEs, adverse events; AI, adrenal insufficiency; AUC, area under the curve; BMI, body mass index; BP, blood pressure; BSA, body surface area; CI, confidence interval; CTX, C-terminal cross-linked telopeptide; DEXA, dual energy X-ray absorptiometry; EES, Efficacy Evaluable Analysis Set; EQ-5D, EQ-5D™ Standardised Health Questionnaire (5-level); FAS, Full Analysis Set; GC, glucocorticoid; HbA1C, Glycated haemoglobin; hsCRP, High sensitivity C-reactive protein; MAF, Multidimensional Assessment of Fatigue; PRA, Plasma renin activity; QoL, quality of life; SDS, standard deviation score; SF-36, Medical Outcome Short Form Health Survey Form 36 (Subject Questionnaire).
Source: Section 8 and 9 of the DIUR-005 Final CSR (dated 30 July 2019)[1] and DIUR-006 CSR Interim Analysis 3 (dated 15 December 2020).[2]

Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Eligibility criteria

DIUR-005

Table 72 presents an overview of the eligibility criteria of DIUR-005. In brief, the study enrolled patients (aged ≥18 years; both genders) with known CAH diagnosed in childhood and elevated 17-OHP and/or A4. Patients were treated at entry in the study with hydrocortisone, prednisone, prednisolone or dexamethasone (or a combination of the aforementioned glucocorticoids) were enrolled. Female patients were required to have negative pregnancy tests; patients who were pregnant would withdraw from the study.

DIUR-006

In DIUR-006, all eligible patients who completed Study DIUR-003 and DIUR-005 could have entered the study; thus, the same eligibility criteria as for DIUR-005 applied to DIUR-006 (Table 72).

Table 72: DIUR-005 and DIUR-006 – eligibility criteria

Trial	Eligibility	
	Inclusion criteria	**Exclusion criteria**
DIUR-005	• Consented patients (aged ≥18 years; both genders) known to have CAH due to 21-OHD (C-CAH) diagnosed in childhood with documented (at any time) elevated 17-OHP and/or A4 and treated at study entry with hydrocortisone, prednisone, prednisolone or dexamethasone (or a combination of these) on a stable GC therapy for a minimum of 6 months • Non-pregnant, non-lactating females who were: – Post-menopausal (defined as at least 12 months natural spontaneous amenorrhoea or at least 6 weeks following surgical menopause); naturally or surgically sterile; of childbearing potential with a negative urinary pregnancy test; and using a medically acceptable method of contraception – Note: females aged ≤55 years presenting with oligomenorrhoea or amenorrhoea were considered potentially fertile and were required to undergo pregnancy testing and use contraception • PRA < 1.5 X ULN at screening or within 3 months prior to screening, except in patients who had been diagnosed with hypertension where the renin was not being used to monitor fludrocortisone replacement	• Co-morbid condition requiring daily administration of a medication (or consumption of any material) that interfered with the metabolism of GCs, including patients on regular daily inhaled, topical, nasal or oral steroids for any indication other than CAH • Clinical or biochemical evidence of hepatic or renal disease. Creatinine over twice the ULN or elevated liver function tests (ALT or AST >2 times ULN) • History of malignancy (other than basal cell carcinoma successfully treated >6 months prior to entry into the study) or any other significant medical or psychiatric conditions that in the opinion of the Investigator would have precluded participation in the trial or patients with a history of bilateral adrenalectomy or having previously been exposed to Efmody • Participation in another clinical study of an investigational or licensed drug or device (excluding current formulation of Efmody) within 3 months prior to inclusion in DIUR-005 • Patients unable to comply with the requirements of the protocol, including patients who routinely

Trial	Eligibility	
	Inclusion criteria	Exclusion criteria
		worked night shifts and so do not sleep during the usual night-time hours
DIUR-006	• Patients with CAH who successfully completed the DIUR-003 or DIUR-005 clinical studies with the current formulation of Efmody • Patients who provided written informed consent	• Same as DIUR-005

Key: 21-OHD, 21-hydroxylase deficiency; 17-OHP, 17-hydroxyprogesterone; A4, Androstenedione; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAH, congenital adrenal hyperplasia; C-CAH, classical congenital adrenal hyperplasia; GC, glucocorticoid; PRA, plasma renin activity; ULN, upper limit of normal.
Source: Section 9.3 of DIUR-005 Final CSR (dated 30 Jul 2019)[28] and Section 9.3 of DIUR-006 CSR Interim Analysis 3 (dated 15 Dec 2020).[30]

Sample size

DIUR-005

A sample size of 102 patients provided greater than 95% power and 2-sided alpha 5% to demonstrate a reduction in the logarithm of the mean daily unsigned SDS of 17-OHP relative to the standard glucocorticoid therapy group (it was assumed that [1] the mean reduction in the Efmody group would be the same as that observed in the Phase II DIUR-003 study, [2] the mean reduction in the standard glucocorticoid therapy group would be approximately 25% of the Efmody Phase II study reduction and [3] the SD of the reduction was the same as that seen in the Phase II study). Thus, 120 patients were to be randomised to the study to account for an inevaluability rate of 15%.
DIUR-005 comprised three analysis sets: Efficacy evaluable analysis set (EES; n=105), Full analysis set (FAS; n=120) and the Safety analysis set (SAS; n=122); see Table 73.

Note: In DIUR-005, all analyses were conducted based on actual treatment received, and not the initial treatment assignment (i.e. ITT). This is because without a precedent for RCTs in CAH (DIUR-005 is the first comparative study of a re-formulation of a standard glucocorticoid therapy for CAH, reflecting the difficulty of conducting trials in this condition) the EES was chosen as the primary analysis set for the evaluation of efficacy, with the robustness of the conclusions being assessed by repeating key efficacy analyses using the FAS.

Table 73: DIUR-005 – pre-defined data sets

Data Analysis Set	Description
Efficacy Evaluable Analysis Set (EES; n=105)	Comprised all patients who were randomised into the study, who received at least one dose of Efmody or standard glucocorticoid therapy, and who had an evaluable Week 24, 17-OHP 24-hour hormone profile, and who had no major protocol violations. Since it is difficult to conduct studies in this indication and this is the first comparative study of a re-formulation of a standard glucocorticoid therapy for CAH, the EES was therefore the primary analysis set for the evaluation of efficacy. The robustness of the conclusions was assessed by repeating key efficacy analyses using the full analysis set (FAS). Patients in the EES were analysed according to the actual treatment received.
Full Analysis Set (FAS; n=120)	Comprised all patients who were randomised into the study, who received at least one dose of Efmody or standard glucocorticoid therapy, and who had at least one evaluable post-randomisation 17-OHP 24-hour hormone profile; patient data were analysed according to the actual treatment received

Safety Analysis Set (SAS; n=122)	Comprised all patients who were randomised into the study and who subsequently received at least one dose of Efmody or standard glucocorticoid therapy; patient data were analysed according to the actual treatment received
Source: Section 9.7.1.1 of the DIUR-005 Final CSR (dated 30 Jul 2019).[28]	

DIUR-006

As DIUR-006 was an open-label extension study designed to gather long-term safety and efficacy data on Efmody, no formal power or sample size calculations were performed. All eligible patients from DIUR-003 (n=16) and DIUR-005 (n=122) could enter DIUR-006 giving a maximum of 138 patients. Patients from DIUR-003 could be enrolled at any time because this study was completed. Patients from DIUR-005 could be enrolled when they completed Visit 4 of DIUR-005. However, in some cases there was a delay between a patient completing DIUR-005 and starting DIUR-006 during which they received standard glucocorticoid therapy. In such cases the patient was entered into DIUR-006 as soon as possible. Two sides from DIUR-005 were unable to continue into DIUR-006 for logistical reasons, and therefore 16 patients from these sites were unable to enrol in the study. Although data for efficacy analysis were collected, no statistical inference testing was planned or performed.

DIUR-006 comprised of patients who received at least one dose of Efmody and completed the Week 24 (Visit 4) assessment or discontinued early from treatment or were withdrawn from the study. As the study is ongoing, all primary, secondary and exploratory endpoints presented within this submission were summarised using the interim analysis Set 3 with patients analysed according to the actual treatment received.

Patient disposition

DIUR-005

In DIUR-005, a total of 138 patients entered into the study, of which 122 were randomised to treatment (Efmody, n=61; standard glucocorticoid therapy, n=61). Of these, 95.9% (n=117/122) of patients completed the 6-month study period of DIUR-005. In total, 88.5% of patients had at least one protocol deviation, with the occurrence of protocol deviations being balanced between the two groups (Table 74).

DIUR-006

As noted in Table 74, sixteen patients completed Study DIUR-003 and 117 patients completed Study DIUR-005, giving a total of 133 patients eligible for enrolment in DIUR-006. Enrolment has now closed, with 92 patients giving informed consent for this extension study. However, one patient was a screen failure, so 91 patients have received at least one dose of Efmody in this open-label extension study and were included in the interim analysis set.

At the time of data cut-off (30 Apr 2020), a total of 91 patients were enrolled in DIUR-006. Of these, 87 entered from DIUR-005 (81 directly and 6 after a gap between completing DIUR-005 and starting DIUR-006 and during which they received non-study glucocorticoid therapy), and four patients entered from DIUR-003 after a gap during which they received non-study glucocorticoid therapy. All patients who entered DIUR-006 after a gap received non-study glucocorticoid therapy during the time of the gap. There were 17 patient withdrawals, with 74 patients remaining on treatment.

DIUR-006 – Disruption due to COVID-19 pandemic

In DIUR-006, a total of 16 patients experienced disruption to their study participation due to the COVID-19 pandemic. Most of the disruptions involved missed assessments, particularly involving assessments that would have been performed at the study centres (e.g. vital signs, DEXA, physical examination, body measurements, laboratory samples). Since most patients had already been in the study for at least 2 years, the later visits incurred the most disruption, particularly at Months 36 and 42. Four patients had home delivery of the investigational medicinal product (IMP) and/or sick day medication to ensure continuity of treatment.

DIUR-005

Patient disposition

Table 74 presents an overview of the patient disposition in DIUR-005.

Table 74: DIUR-005 patient disposition

	Number (%) of patients		
	Efmody®	**Standard GC therapy**	**Total**
Patients enrolled[a]	-	-	138
Patients who were not randomised[b]	-	-	16 (100.0)
Patient request	-	-	1 (6.3)
Screen failure	-	-	13 (81.3)
Physician or Sponsor request	-	-	1 (6.3)
Other	-	-	1 (6.3)
Patients randomised	61 (100.0)	61 (100.0)	122 (100.0)
Patients who received at least one dose of IMP[c]	61 (100.0)	61 (100.0)	122 (100.0)
Patients who did not receive at least one dose of IMP[c]	0	0	0
Patients who withdrew early[d,e]	3 (4.9)	2 (3.3)	5 (4.1)
Withdrawn due to an AE	1 (1.6)	0	1 (0.8)
Withdrawn due to Physician or Sponsor request	0	1 (1.6)	1 (0.8)
Withdrawn due to a participant request	2 (3.3)	1 (1.6)	3 (2.5)
Patients who completed treatment[d]	58 (95.1)	59 (96.7)	117 (95.9)
Patients continuing into extension study[d]	44 (72.1)	42 (68.9)	86 (70.5)

Key: AE, adverse event; GC, glucocorticoid; IMP, investigational medicinal product.
Note: [a], Informed consent received; [b], Percentages are calculated from the number of patients who were not randomised; [c], Percentages are calculated from the number of patients randomised; [d], Percentages are calculated from the number of patients who received at least one dose of IMP; [e], Excludes patients who completed treatment.
Source: Merke et al. 2021[18] and Table 4 of DIUR-005 Final CSR (dated 30 Jul 2019).[19]

Demographics, baseline disease characteristics and concomitant medications

Table 75 presents an overview of the patient demographics and baseline disease characteristics in DIUR-005 both of which were similar in the two treatment groups. Across the trial, the mean age of patients was 36.3 years, and the majority of patients were white (98.4%) and female (63.9% versus 36.1% for men). The most frequently used prior CAH medication was hydrocortisone (61.5%), with prednisolone being the second most common treatment (35.2%). Only a small number of patients were taking prednisone (4.1%) or dexamethasone (8.2%). In the year prior to entry into the study (before patients were randomised to start Efmody or continue standard glucocorticoid therapy), three patients (Efmody, n=2; standard glucocorticoid therapy, n=1) had been hospitalised and five patients (Efmody, n=3; standard glucocorticoid therapy, n=2) had an adrenal crisis). Medical histories other than CAH (overall, 82.8%) were generally similar in both treatment groups; depression (overall, 15.6%) followed by Vitamin D deficiency (overall, 12.3%) were the most common (Table 75).

Table 75: DIUR-005: Demographic and baseline disease characteristics (SAS)

Characteristic	Number (%) of patients		
	Efmody (n=61)	Standard GC therapy (n=61)	Total (n=122)
Age (years)			
Mean (SD)	35.2 (10.3	37.5 (12.8)	36.3 (11.6)
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	5 (8.2)	12 (19.7)	17 (13.9)
≥70	0	0	0
Gender, n (%)			
Male	19 (31.1)	25 (41.0)	44 (36.1)
Female	42 (68.9)	36 (59.0)	78 (63.9)
Race, n (%)			
White	60 (98.4)	60 (98.4)	120 (98.4)
Other	1 (1.6)	1 (1.6)	2 (1.6)
BMI (kg/m^2)			
Mean (SD)	28.5 (6.4)	27.7 (4.3)	28.1 (5.4)
Median (range)	27.8 (18.0–43.7)	27.0 (19.7–36.8)	27.1 (18.0–43.7)
Waist circumference (cm)			
Mean (SD)	90.9 (16.3)	90.5 (11.8)	90.7 (14.2)
Median (range)	89.0 (63.0–133.0)	86.0 (73.0–119.0)	88.0 (63.0–133.0)
Time since CAH diagnosis (years)			
Mean (SD)	33.7 (10.2)	36.6 (12.6)	35.2 (11.5)
Median (range)	33.5 (17–60)	35.7 (13–65)	34.4 (13–65)
Hospitalised within last 12 months prior to enrolment into DIUR-005, n (%)			
No	59 (96.7)	60 (98.4)	119 (97.5)
Yes	2 (3.3)	1 (1.6)	3 (2.5)
Number of adrenal crises in the last year, n (%)			
None	58 (95.1)	59 (96.7)	117 (95.9)
One	3 (4.9)	2 (3.3)	5 (4.1)
Prior CAH medication, n (%)			
Hydrocortisone	36 (59.0)	39 (63.9)	75 (61.5)
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)

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Key: BMI, body mass index; CAH, congenital adrenal hyperplasia; GC, glucocorticoid; SD, standard deviation; n, number of evaluable patients
Note: Patients who received more than one medication in the last 6 months were counted once per category
Source: Merke et al. 2021[18] and Tables 7 and 8 of DIUR-005 Final CSR (dated 30 Jul 2019)[19]

All patients reported use of at least one concomitant medication during the study, with the most common medication being fludrocortisone (reported by 85.2% of patients overall). Use of most other medications was similar in the two treatment groups, although slightly more patients used paracetamol and colecalciferol in the Efmody group compared to the standard glucocorticoid therapy group (paracetamol: 37.7% versus 24.6%; colecalciferol: 26.2% versus 14.8%). Overall, 22.1% of patients used other steroid medications not from the sick day packs, with the most common medication taken being hydrocortisone (Efmody, 9.8%; standard glucocorticoid therapy, 18.0%).

DIUR-006

Patient disposition

Table 76 presents an overview of the patient disposition in DIUR-006. A total of 91 patients have been enrolled; of these, 87 entered from Study DIUR-005, 81 directly and 6 after a gap between completing Study DIUR-005 and starting Study DIUR-006, and 4 patients entered from DIUR-003 after a gap. Those who entered the study after a gap received non-study glucocorticoid therapy during this time. At the time of data cut-off (30 Apr 2020), there were 17 patient withdrawals, with 74 patients remaining on treatment.

Table 76: DIUR-006 patient disposition

	Overall DIUR-006	**DIUR-005 No gap**		**DIUR-005 Gap**	**DIUR-003**
	Efmody (N=92), n (%)	**Efmody (N=41), n (%)**	**Standard GC therapy (N=40), n (%)**	**Non-study GC therapy (N=6), n (%)**	**Non-study GC therapy (N=5), n (%)**
Enrolled[a]	92	41	40	6	5
Assigned to treatment[b]	91 (100.0)	41 (100.0)	40 (100.0)	6 (100.0)	4 (100.0)
Received ≥1 dose Efmody[c]	91 (98.9)	41 (100.0)	40 (100.0)	6 (100.0)	4 (80.0)
Ongoing treatment at data cut-off[d]	74 (81.3)	34 (82.9)	31 (77.5)	5 (83.3)	4 (100.0)
Withdrew early at data cut-off[d]	17 (18.7)	7 (17.1)	9 (22.5)	1 (16.7)	0
Adverse event	2 (2.2)	0	2 (5.0)	0	0
Pregnancy	2 (2.2)	1 (2.4)	1 (2.5)	0	0
Physician or sponsor request	2 (2.2)	2 (4.9)	0	0	0
Patient request	10 (11.0)	3 (7.3)	6 (15.0)	1 (16.7)	0
Other	1 (1.1)	1 (2.4)	0	0	0

Key: GC, glucocorticoid.
Notes: [a], Informed consent received for DIUR-006; [b], Percentages are calculated from the number of participants who were enrolled; [c], Percentages are calculated from the number of participants who were assigned to treatment; [d], Percentages are calculated from number of participants who received at least one dose of Efmody.
Data cut-off: 30 Apr 2020.
Source: Table 3. DIUR-006 CSR Interim Analysis 3 (dated 15 Dec 2020).[20]

Disruption due to COVID-19 pandemic

A total of 16 patients experienced disruption to their study participation due to the COVID-19 pandemic. Most of the disruptions involved missed assessments, particularly involving assessments that would have been performed at the study centres (e.g. vital signs, DEXA, physical examination, body measurements, laboratory samples). Since most patients had already been in the study for at least 2 years, the later visits incurred the most disruption, particularly at Months 36 and 42. Four patients had home delivery of IMP and/or sick day medication to ensure continuity of treatment (refer to DIUR-006 CSR).

Demographics, baseline disease characteristics and concomitant medications

Table 77 presents an overview of the patient demographics and baseline disease characteristics in DIUR-006 and by feeder study. Just under half of patients (45.1%) were receiving Efmody therapy within the 12 months prior to enrolment due to their previous randomisation in Study DIUR-005. Other therapies patients were receiving prior to study entry were hydrocortisone (44.0%), prednisolone (18.7%), dexamethasone (4.4%) and prednisone (3.3%).

Table 77: DIUR-006 patient demographics (Interim Analysis Set)

	Overall DIUR-006	**DIUR-005 No gap**		**DIUR-005 Gap**	**DIUR-003**
	Efmody (N=91)	**Efmody (N=41)**	**Standard GC therapy (N=40)**	**Non-study GC therapy (N=6)**	**Non-study GC therapy (N=4)**
Age (years					
Mean (SD)	37.1 (11.8)	37.1 (10.6)	37.8 (12.9)	35.3 (12.6)	33.8 (14.4)
Median (range)	35.0 (20, 67)	36.0 (20, 61)	37.0 (20, 67)	32.5 (23, 50)	28.5 (23, 55)
Age group (years), n (%)					
≥18–<30	30 (33.0)	11 (26.8)	13 (32.5)	3 (50.0)	3 (75.0)
≥30–<50	44 (48.4)	25 (61.0)	18 (45.0)	1 (16.7)	0
≥50–<70	17 (18.7)	5 (12.2)	9 (22.5)	2 (33.3)	1 (25.0)
≥70	0	0	0	0	0
Gender, n (%)					
Male	29 (31.9)	13 (31.7)	15 (37.5)	0	1 (25.0)
Female	62 (68.1)	28 (68.3)	25 (62.5)	6 (100.0)	3 (75.0)
Race, n (%)					
White	89 (97.8)	40 (97.6)	40 (100.0)	6 (100.0)	3 (75.0)
BMI (kg/m^2)					
Mean (SD)	28.8 (5.7)	29.5 (6.6)	28.8 (4.5)	26.0 (4.9)	25.3 (5.9)
Median (range)	28.3 (18.0, 43.7)	28.3 (18.0, 43.7)	29.3 (20.8, 37.6)	26.5 (20.1, 33.6)	23.5 (20.3, 33.8)
Waist Circumference (cm)					
Mean (SD)	91.5 (14.8)	92.1 (16.6)	92.1 (13.0)	84.7 (12.4)	91.1 (19.5)
Median (range)	89.0 (65.0, 133.0)	89.0 (65.0, 133.0)	90.3 (72.0, 120.0)	89.0 (66.0, 98.0)	85.1 (74.8, 119.2)
Time since CAH diagnosis (years)					
Mean (SD)	35.8 (11.6)	35.3 (10.4)	36.8 (12.6)	34.0 (12.0)	33.1 (15.4)
Median (range)	33.9 (17.1, 65.8)	34.4 (17.4, 60.0)	34.0 (17.1, 65.8)	32.4 (21.7, 50.6)	28.7 (19.6, 55.3)

	Overall DIUR-006	DIUR-005 No gap		DIUR-005 Gap	DIUR-003
	Efmody (N=91)	Efmody (N=41)	Standard GC therapy (N=40)	Non-study GC therapy (N=6)	Non-study GC therapy (N=4)
Hospitalised within last 12 months prior to enrolment into DIUR-006, n (%)					
No	85 (93.4)	37 (90.2)	38 (95.0)	6 (100.0)	4 (100.0)
Yes	6 (6.6)	4 (9.8)	2 (5.0)	0	0
Number of adrenal crises in the last year, n (%)					
None	86 (94.5)	39 (95.1)	37 (92.5)	6 (100.0)	4 (100.0)
One	5 (5.5)	2 (4.9)	3 (7.5)	0	0
Prior CAH medication, n (%)					
Efmody	41 (45.1)	41 (100.0)	0	0	0
Hydrocortisone	40 (44.0)	9 (22.0)	25 (62.5)	4 (66.7)	2 (50.0)
Prednisolone	17 (18.7)	0	15 (37.5)	2 (33.3)	0
Dexamethasone	4 (4.4)	0	4 (10.0)	0	0
Prednisone	3 (3.3)	0	1 (2.5)	0	2 (50.0)

Key: GC, glucocorticoid.
Notes: Patients who received more than one medication in the last 12 months were counted once per category.
Data cut-off: 30 Apr 2020.
Source: Table 6 and Table 7.DIUR-006 CSR Interim Analysis 3 (dated 15 Dec 2020).[20]

All patients reported use of at least 1 concomitant medication during the study (100.0%), with the most common medication being fludrocortisone/fludrocortisone acetate (85.7% overall), followed by paracetamol (36.3% overall), colecalciferol/Vitamin D (31.9% overall), and ibuprofen (24.2% overall).

Comparability of patients across studies

Not applicable as DIUR-006 is long-term extension study of the pivotal Phase III DIUR-005 study meaning that patients are comparable across key studies.

Comparability of the study populations with Danish patients eligible for treatment

Danish trial site included in the pivotal Phase III DIUR-005 trial; hence, study population is considered comparable with the Danish patients eligible for Efmody. Please see Sections 7 and 8 for further information.

Appendix D Efficacy and safety results

Additional efficacy data - Disease control: 17-OHP and A4

Table 78: DIUR-005 – *post-hoc* analysis: absolute values and changes from baseline for the primary efficacy variable of 17-OHP at baseline and week 24 (EES)

Group	Time point	N	Mean	SD	Min	Median	Max
Absolute values							
Efmody	Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Visit 4/ Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard GC therapy	Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Visit 4/Week 42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							
Efmody	Visit 2/ Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard GC therapy	Visit 2/ Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: 17-OHP, 17-hydroxyprogesterone; EES, efficacy evaluable analysis set; GC, glucocorticoid; SD, standard deviation.
Source: *Post-hoc* analyses. Table 23. DIUR-005 Final CSR (dated 30 July 2019).[1]

Table 79: DIUR-005 – responders at 09.00 hours at week 24 for 17-OHP and A4 (EES)

Group	N	Number (%) of patients with a response[a,b]	Adjusted response rate (%)	Comparison between groups		
				Odds ratio	95% CI	2-sided p-value
17-OHP						
Efmody	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard GC therapy	[redacted]	[redacted]	[redacted]			
[redacted]						
Efmody	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Standard GC therapy	[redacted]	[redacted]	[redacted]			

Key: 17-OHP, 17-hydroxyprogesterone; A4, androstenedione; CI, confidence interval; EES, efficacy evaluable analysis set; GC, glucocorticoid.
Notes: [a]A patient 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. [b]Logistic regression model was used to evaluate responders. An odds ratio >1 favours Efmody. 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).
Source: Secondary endpoint. Table 29. DIUR-005 Final CSR (dated 30 July 2019).[1]

Table 80: DIUR-006 – change from pre-Efmody baseline in SDS at 09.00 and 13.00 hours (Interim Analysis Set)

Time point	n	Mean	SD	Min	Median	Max
17-OHP 09:00 SDS						
Visit 2/Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 3/Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 4/Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 5/Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 6/Month 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 7/Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 8/Month 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 9/Month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 10/Month 42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
17-OHP 13:00 SDS						
Visit 2/Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 3/Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 4/Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 5/Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 6/Month 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 7/Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 8/Month 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 9/Month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 10/Month 42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A4 SDS 09:00 SDS						
Visit 2/Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 3/Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Time point	n	Mean	SD	Min	Median	Max
Visit 4/Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 5/Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 6/Month 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 7/Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 8/Month 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 9/Month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 10/Month 42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
A4 SDS 13:00 SDS						
Visit 2/Week 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 3/Week 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 4/Week 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 5/Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 6/Month 18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 7/Month 24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 8/Month 30	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 9/Month 36	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 10/Month 42	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: 17-OHP, 17-hydroxyprogesterone; A4, androstenedione; SD, standard deviation; SDS, standard deviation score.
Notes: Pre-Efmody baseline means prior to the first dose of Efmody which was the reassessed baseline under DIUR-006 for patients entering from Study DIUR-003 and Study DIUR-005 after a gap; Visit 4 (Week 24) from the feeder study for patients who received standard GC therapy in Study DIUR-005 with no gap, and prior to the first Efmody dose in Study DIUR-005 for patients who received Efmody in Study DIUR-005 with no gap (i.e. DIUR-005 baseline visit).The SDSs are calculated by counting the number of SDs which are above or below the mean of the log transformed range.
Data cut-off: 30 April 2020.
Source: Secondary endpoint (efficacy). Table 17. DIUR-006 CSR Interim Analysis 3 (dated 15 December 2020).[2]

Number of patients		Overall DIUR-006	DIUR-005 No Gap		DIUR-005 Gap	DIUR-003
		Efmody (N=91) n (%)	Efmody (N=41) n (%)	Standard GC therapy (N=40) n (%)	Non-study GC therapy (N=6) n (%)	Non-study GC therapy (N=4) n (%)
Visit 2/ Week 4	On treatment, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Requiring adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dose increase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning and evening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evening only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dose decrease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning and evening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evening only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 3/ Week 12	On treatment, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Requiring adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dose increase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning and evening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evening only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dose decrease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning and evening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evening only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 4/ Week 24	**On treatment, n**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Requiring adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dose increase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning and evening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evening only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dose decrease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning and evening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evening only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 5/ Month 12	**On treatment, n**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Requiring adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dose increase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Number of patients		Overall DIUR-006	DIUR-005 No Gap		DIUR-005 Gap	DIUR-003
		Efmody (N=91) n (%)	Efmody (N=41) n (%)	Standard GC therapy (N=40) n (%)	Non-study GC therapy (N=6) n (%)	Non-study GC therapy (N=4) n (%)
	Morning and evening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evening only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dose decrease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning and evening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evening only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 6/ Month 18	**On treatment, n**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Requiring adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dose increase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning and evening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evening only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dose decrease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning and evening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evening only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 7/ Month 24	**On treatment, n**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Requiring adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dose increase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning and evening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evening only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dose decrease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning and evening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evening only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 8/ Month 30	**On treatment, n**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Requiring adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dose increase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Number of patients		Overall DIUR-006	DIUR-005 No Gap		DIUR-005 Gap	DIUR-003
		Efmody (N=91) n (%)	Efmody (N=41) n (%)	Standard GC therapy (N=40) n (%)	Non-study GC therapy (N=6) n (%)	Non-study GC therapy (N=4) n (%)
	Morning and evening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evening only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dose decrease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning and evening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evening only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 9/ Month 36	On treatment, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Requiring adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dose increase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning and evening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evening only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dose decrease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning and evening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evening only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visit 10/ Month 42	On treatment, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Requiring adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dose increase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning and evening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evening only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Dose decrease	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning and evening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Morning only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Evening only	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: GC, glucocorticoid; n, number of evaluable patients.
Notes: Percentages are calculated from the number of patients on treatment.
Data cut-off: 30 April 2020.
Source: Secondary endpoint (efficacy). Table 24. DIUR-006 CSR Interim Analysis 3 (dated 15 December 2020).[2]

DIUR-006: incidence of dose titrations

Table 81: DIUR-006 – dose titrations (Interim Analysis Set)

Body composition

Table 82: DIUR-006 – change from pre-Efmody baseline to month 36 in body composition (DEXA) (Interim Analysis Set)

Time point (visit)	N	Bone mineral density (g/cm^2)	Total fat mass (kg)	Total lean mass (kg)	T-score	Z-score
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
36 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: DEXA, dual energy X-ray absorptiometry.
Notes: German patients were excluded from this table as DEXA scans were not performed at German sites.
Data cut-off: 30 April 2020.
Source: Secondary endpoint (efficacy). TFL Table 14.2.4.2. DIUR-006 CSR Interim Analysis 3 (dated 15 December 2020).[2]

Quality of life

Table 83: DIUR-005 - quality of life assessments (Efficacy Evaluable Set)

Parameter	Efmody (N=53)	Standard glucocorticoid therapy (N=52)
SF-36 absolute change from baseline by domain[a]		
T score: bodily pain[b]	NA	NA
T score: general health perceptions	0.79 (7.54)	-1.88 (5.97)
T score: mental health	0.86 (7.32)	0.35 (7.81)
T score: physical functioning	1.16 (6.43)	-0.52 (4.27)
T score: role emotional	0.99 (9.95)	-0.34 (9.21)
T score: role physical	1.91 (8.33)	0.50 (6.68)
T score: social functioning	2.18 (9.25)	0.87 (6.86)
T score: vitality	0.79 (9.45)	0.92 (6.10)
Global Fatigue Index absolute change in score from baseline		
GFI score derived from MAF	-0.74 (11.1)	-0.26 (7.8)
EQ-5D summary changes from baseline		
EQ-5D VAS score	-1.3 (13.67)	-1.2 (12.62)
EQ-5D-5L index score	0.02 (0.12)	0.02 (0.14)

Key: EQ-5D, Standardized Health Questionnaire (5L=5-level); GFI, Global Fatigue Index; MAF, multidimensional assessment of fatigue; N, number of evaluable participants; NA, not available; SF-36, Medical Outcome Short Form Health Survey Form 36 (Subject Questionnaire); VAS, visual analog scale.
Notes: Values are mean (SD). GFI scores range from 1 (no fatigue) to 50 (severe fatigue). [a]Baseline is defined as start of study in the phase 3 study and pre–Efmody initiation baseline in the safety extension study. [b]A technical issue with the scoring of the bodily pain domain meant that these data are not available.
Data cut-off: 30 April 2020.
Source: Adapted from Table 6 of Merke et al 2021.[3]

Appendix E Safety data for intervention and comparator(s)

Extent of exposure

Table 84: DIUR-005-duration of exposure (Safety Analysis Set)

Treatment duration	Statistics	Efmody (n=61)	Standard GC therapy (n=61)
Total treatment duration (days)[a]	Mean (SD)	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]
	Total treatment years[b]	[redacted]	[redacted]
Actual treatment duration (days)[c]	Mean (SD)	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]
	Total treatment years[b]	[redacted]	[redacted]

Key: GC, glucocorticoid; SD, standard deviation.
Notes: [a]Total treatment duration=(last dose date - first dose date +1). [b]The total treatment years duration calculated by adding the durations for each patient in the treatment group. [c]Actual treatment duration= total treatment duration, excluding dose interruptions.
Source: Table 15. DIUR-005 Final CSR (dated 30 July 2019).[1]

Table 85: DIUR-006–duration of exposure (Interim Analysis Set)

Treatment duration		Overall DIUR-006	DIUR-005 No gap		DIUR-005 Gap	DIUR-003
		Efmody (N=91)	Efmody (N=41)	Standard GC therapy (N=40)	Non-study GC therapy (N=6)	Non-study GC therapy (N=4)
During Study DIUR-006 only						
Total treatment duration (days)[a]	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total treatment, years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Actual treatment duration (days)[b]	Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Total treatment, years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative continuous exposure in DIUR-005 and DIUR-006 only						
Total treatment duration (days)[c]	Mean (SD)	[redacted]	[redacted]	[redacted]	N/A	N/A
	Median (range)	[redacted]	[redacted]	[redacted]	N/A	N/A
	Total treatment, years	[redacted]	[redacted]	[redacted]	N/A	N/A

Treatment duration		Overall DIUR-006	DIUR-005 No gap		DIUR-005 Gap	DIUR-003
		Efmody (N=91)	Efmody (N=41)	Standard GC therapy (N=40)	Non-study GC therapy (N=6)	Non-study GC therapy (N=4)
Actual treatment duration (days)[d]	Mean (SD)	[redacted]	[redacted]	[redacted]	N/A	N/A
	Median (range)	[redacted]	[redacted]	[redacted]	N/A	N/A
	Total treatment, years	[redacted]	[redacted]	[redacted]	N/A	N/A

Key: GC, glucocorticoid; N/A, not applicable; SD, standard deviation.
Notes: [a]Total treatment duration=last dose date of Efmody in DIUR-006 - first dose date in DIUR-006 +1. [b]Actual treatment duration=total number of days in which the patient took at least 1 dose of Efmody in DIUR-006. [c]Cumulative total treatment duration=(last dose date of Efmody in DIUR-006 - first dose date in DIUR-006 or DIUR-005+1). [d]Cumulative actual treatment duration=total number of days in which the patient took at least 1 dose of Efmody in either DIUR-005 or DIUR-006. The total treatment years duration was calculated by adding the durations for each patient in the treatment group.
Data cut-off: 30 April 2020.
Source: Table 12. DIUR-006 CSR Interim Analysis 3 (dated 15 December 2020).[2]

Frequent adverse events

Table 86: DIUR-005 – most common AEs (occurring in >5% patients) (SAS)

System organ class: preferred term	Number (%) of participants[a]	
	Efmody (N=61)	Standard GC therapy (N=61)
Participants with any AE	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Viral upper respiratory tract infection	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]
General disorders and administration site conditions	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Therapeutic response unexpected	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Malaise	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Influence-like illness	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]
Headache	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]

System organ class: preferred term	Number (%) of participants[a]	
	Efmody (N=61)	Standard GC therapy (N=61)
Abdominal pain upper	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	[redacted]	[redacted]
Back pain	[redacted]	[redacted]
Metabolism and nutrition disorders	[redacted]	[redacted]
Increase appetite	[redacted]	[redacted]
Psychiatric disorders	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Investigations	[redacted]	[redacted]
Renin increased	[redacted]	[redacted]
Blood and lymphatic system disorders	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]

Key: AE, adverse event; GC, glucocorticoid; SAS, safety analysis set.
Notes: [a]Number (%) of patients with at least 1 AE
Source: Table 48. DIUR-005 Final CSR (dated 30 July 2019).[1]

Table 87: DIUR-006 – most common AEs (occurring in >10% patients) (Interim Analysis Set)

AE category (preferred term)	Number (%) of patients[a]				
	Overall DIUR-006	DIUR-005 No gap		DIUR-005 Gap	DIUR-003
	Efmody (N=91)	Efmody (N=41)	Standard GC therapy (N=40)	Non-study GC therapy (N=6)	Non-study GC therapy (N=4)
Participants with any AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Influenza	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastroenteritis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Therapeutic response unexpected	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain in extremity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE category (preferred term)	Number (%) of patients[a]				
	Overall DIUR-006	DIUR-005 No gap		DIUR-005 Gap	DIUR-003
	Efmody (N=91)	Efmody (N=41)	Standard GC therapy (N=40)	Non-study GC therapy (N=6)	Non-study GC therapy (N=4)
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AE, adverse event; GC, glucocorticoid.
Notes: [a]Number (%) of patients with at least 1 AE. [b]Includes 1 patient for whom 'Nasopharyngitis' was incorrectly coded under SOC 'Respiratory, thoracic and mediastinal disorders'.
Data cut-off: 30 April 2020.
Source: Table 29. DIUR-006 CSR Interim Analysis 3 (dated 15 December 2020).[2]

Appendix F Comparative analysis of efficacy and safety

Not applicable as additional comparative analysis was not conducted.

Appendix G Extrapolation

Not applicable as additional data extrapolation was not conducted.

Appendix H Literature search for HRQoL data

Targeted literature searches including HRQoL search utilized in the cost-effectiveness model presented in final TLR reports.[75, 76]

In addition, final TLR reports can be found here:

TLR on biomarkers: 2846_Diurnal Chronocort_Task 9 Tl

TLR on GC dose: 2846_Diurnal Chronocort_Task 10 -

Targeted literature search (TLR) methodology is described below.

Objective:
The objective of the TLR was to perform a review of the published literature to contribute to the early cost-effectiveness model for Efmody. The TLR identified links between biomarkers (captured in the clinical trial programme – androgen and cortisol levls) to key outcomes for CAH that are of prime concern to payers, such as quality of life (QoL).

Approach - database searches:

To do so, the following electronic databases were searched:

- MEDLINE® In-Process (using Pubmed.com)
- Embase® and MEDLINE (using Embase.com)
- The Cochrane Library (using Cochranelibrary.com), including:
  - The Cochrane Database of Systematic Reviews (CDSR)
  - The Database of Abstracts of Reviews of Effectiveness (DARE)
  - The Cochrane Central Register of Controlled Trials (CENTRAL)
  - Health Technology Assessment Database (HTAD)

Electronic searching in the literature databases was conducted to include all recent publications published after the original TLR to include publications from 2017 and onwards.
Grey literature search:
In addition to the database searches, relevant websites were searched for further information such as potential conference abstracts, posters, and webpages. Furthermore, a manual search of the reference lists of relevant articles was conducted for frequently cited or important historical articles. In the updated TLR, websites (including relevant health technology assessment [HTA] websites etc.) and conference proceedings were checked for last 2 years to add continuity to the original TLR.
Websites and conference proceedings included following:

- World Health Organization (WHO)
- European Society of Paediatric Endocrinology (ESPE)
- European Society of Endocrinology (ESE)/European Congress of Endocrinology (ECE)
- The Endocrine Society (ENDO)
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual European Congress
- ISPOR Annual International Congress

Key international HTA bodies searched for HTAs, included:

- In the UK:
  - National Institute for Health and Care Excellence (NICE)
  - Scottish Medicines Consortium (SMC)
  - All Wales Medicines Strategy Group (AWMSG)
- In Europe: examples include:
  - Dental and Pharmaceutical Benefits Board (TLV) in Sweden
  - Zorginstituut Nederland (ZIN) in The Netherlands
  - The Federal Joint Committee, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) in Germany
  - Haute Autorité de Santé (HAS) in France
  - Also, HTAs from Spain, Italy, Norway, Denmark, and Austria were searched within the International Network of Agencies for Health Technology Assessment (INAHTA)
- Outside of Europe:
  - Pharmaceutical Benefits Advisory Committee (PBAC) in Australia
  - Canadian Agency for Drugs and Technologies in Health (CADTH)
  - Israel Center for Technology Assessment in Health Care (ICTAHC)
  - New Zealand Health Technology Assessment (NZHTA)
  - Health Insurance Review and Assessment Service (HIRA) in Korea
- International Network of Agencies for Health Technology Assessment (INAHTA) to search for all HTAs in the countries of interest (to act as a cross-check with those above)

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- An attempt was made to search non-English HTAs from regions including Japan, Taiwan, and China. However, due to language restrictions, it was not possible to identify any relevant HTAs. BresMed advises Diurnal to utilize their in-house language experts to identify these sources, if possible.

Study selection:
Potentially relevant publications were reviewed and assessed to collate a final set of studies that formed the main body of the clinical evidence. To determine the final set of studies eligible for review, inclusion and/or exclusion criteria was applied to the literature search results.
Study selection criteria:
The inclusion and exclusion criteria are specified in Table 88 and were applied to the literature search results to identify the final set of studies that were utiised in th health-economic model.

Table 88: Inclusion and exclusion criteria

Category	Inclusion criteria	Exclusion criteria
Population	Adolescent ≥ 12 years and adult population in any of the following disease areas: • CAH • Adrenal insufficiency/failure: – Addison's disease – Autoimmune AI – Autoimmune polyendocrine syndromes – Adrenoleukodystrophy – Hypoaldosteronism – Waterhouse–Friderichsen syndrome Please note that due to scarcity of data on correlation between biomarkers and fertility outcomes, additional disease areas were explored including PCOS, PCOD, HAIR-AN syndrome, and patients with irregular menses – by conducting a grey literature search	Healthy volunteers
Outcomes	Relationship between at least one of the following clinical outcomes measured in Chronocort® trials: • Cortisol levels • Androgens With any of the outcomes of greater interest to payers: • Mortality • Survival • QoL (including caregiver burden) • Infertility • Adrenal crises and sequelae • Fat mass and lean body weight • Bone density, osteoporosis, osteopenia, fracture • Body mass index and waist circumference • Insulin, haemoglobin a1c, glucose sensitivity, glucose tolerance, glucose intolerance, insulin resistance, glucose intolerance, insulin resistance • Sick day rules (sick day dosing, stress dosing, emergency dosing) • Plasma renin activity • High sensitivity C- reactive protein • Monitoring, compliance, and adherence • Cardiovascular disease, hypertension • Hyperlipidaemia • Hospitalization • Pregnancy, oligomenorrhea, hypomenorrhea, spaniomenorrhea, and amenorrhea	No information is reported for any of the topics of interest

	• Short stature	
Study design and publication types	Any studies that report a link between clinical outcomes measured in Chronocort® trials and outcomes of interest for the model (those of greater relevance for payers)	• Case reports • In vitro studies • Animal studies The following publication types were excluded: • Letters • Comments • Editorials • News articles
Language	English@	Articles in a language that cannot be translated in-house
Country	All	None
Key: AI, adrenal insufficiency; CAH, congenital adrenal hyperplasia; QoL, quality of life; TLR, targeted literature review.		

Desk research:
Desk research involved collecting data from available official sources in Denmark for costs and general population inputs of the cost-effectiveness model i.e. Denmark DRG tariff 2021, MEDICINPRISER.DK, Denmark statistics, Denmark Population (2021) – Worldometer and Danish Heart Statistics.

Economic systematic literature review (SLR) methodology is described below, and final economic SLR report is embedded in Appendix A:

The objective of the de novo economic systematic literature review (SLR) was to identify published economic models, available economic evidence including economic evaluations, costs, and resource use, as well as relevant utility and health-related quality of life ([HRQL]; 36-Item Short Form Survey [SF-36] and EQ-5D® only) data for patients with CAH. The specific objectives were:

- To identify published economic models and cost-effectiveness studies in CAH to inform the development of an economic model for MR-HC (Chronocort®)
- To identify the burden of illness in terms of cost and resource use evidence in CAH
- To identify the utility evidence in CAH to inform an economic model for MR-HC (Chronocort®)

Electronic and manual searches
Database searches
The following electronic databases were searched (i.e., standard evidence sources used in health technology assessments [HTAs]):

- MEDLINE® In-Process (using Pubmed.com)
- Embase® and MEDLINE (using Embase.com)
- EconLit
- Centre for Reviews and Dissemination York (archived records until 2015), for the following:
  - Health Technology Assessment Database
  - National Health Service Economic Evaluation Database

Grey literature searches
Conference proceedings were also searched for 2 years (2018–2019) to identify the abstracts of interest.
The following conferences were searched for the economic SLRs:

- European Society of Endocrinology/European Congress of Endocrinology
- The Endocrine Society
- International Society for Pharmacoeconomics and Outcomes Research
- Society for Endocrinology (SfE BES)

Submission documents from the following HTA agencies were reviewed for relevant economic data:

- In the UK:
  - National Institute for Health and Care Excellence (NICE)
  - Scottish Medicines Consortium (SMC)
  - All Wales Medicines Strategy Group (AWMSG)
- In Europe: examples include:
  - Dental and Pharmaceutical Benefits Board (TLV) in Sweden
  - Zorginstituut Nederland (ZIN) in The Netherlands
  - The Federal Joint Committee, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) in Germany
  - Haute Autorité de Santé (HAS) in France
  - Also, HTAs from Spain, Italy, Norway, Denmark, and Austria searched within the International Network of Agencies for Health Technology Assessment (INAHTA)
- Outside of Europe:
  - Pharmaceutical Benefits Advisory Committee (PBAC) in Australia
  - Canadian Agency for Drugs and Technologies in Health (CADTH)
- International Network of Agencies for Health Technology Assessment (INAHTA) to search for all HTAs within the countries of interest (to act as a cross-check with those above)
- Commission on Environmental, Economic and Social Policy (CEESP)

Two conferences were not searched due to unavailability of their English versions:

- Société Française d'Endocrinologie (SFE) – France
- SEEN Congress

Study selection criteria
Systematic literature review of economic evaluation studies

in terms of population, interventions, comparators, outcomes, study type and others.

Category	Inclusion criteria	Exclusion criteria
Population	• Adult and adolescent (age ≥12 years) patients with CAH	• Healthy volunteers • Patient population without CAH • Patients with non-classical CAH

Category	Inclusion criteria	Exclusion criteria
Interventions	• No restrictions	None
Comparators	• No restrictions	None
Outcomes	• QALYs/incremental QALY • DALYs/incremental DALY • LYs/incremental LYs • ICER • Model summary (including perspective, time horizon and discounting) and structure • Any other measure of effectiveness reported together with costs • Sources of clinical, cost, resource use and utility inputs • Time horizon • Cycle length • Sensitivity analysis (including variability reported around the parameters) and model assumptions	• Studies not reporting model outputs • Studies reporting clinical data only
Study type	Full economic evaluations/models/HTA evaluations: • Cost consequence • Cost–minimization • Cost effectiveness • Cost–utility • Cost–benefit • Budget impact • Systematic reviews[a]	• Letters, comments and editorials • Simple costing analysis studies
Time limit	2000 to present	None
Language	English language only	None
Countries	No limit	None
Key: CAH, congenital adrenal hyperplasia; DALYs, disability-adjusted life years; HTA, health technology assessment; ICER, incremental cost-effectiveness ratio; LYs, life years; QALYs, quality-adjusted life years; SLR, systematic literature review. **Notes**: [a], systematic reviews were included and flagged for bibliography searches		

Systematic literature review of cost and resource use studies

The inclusion and exclusion criteria for cost and resource use studies are specified in Table 90 in terms of population, interventions, comparators, outcomes, study type and others.

Category	Inclusion criteria	Exclusion criteria
Population	Adults and adolescents (age ≥12 years) with CAH	• Healthy volunteers • Patient population without CAH • Patients with non-classical CAH
Interventions	No limit	None
Comparators	No limit	None

Category	Inclusion criteria	Exclusion criteria
Outcomes	Cost and resource use data such as: • Any direct costs • Any indirect costs • Any resource costs • Indirect costs including productivity costs • Total costs • Length of hospitalization/hospital stay • Physician visits • Primary care costs • Secondary care costs • Community care costs • Sources of cost and resource inputs	Clinical outcomes
Study type	• Cost and resource use studies • Cost studies • Resource use studies • Economic evaluations • Systematic reviews[a]	Letters, comments, and editorials
Time limit	2000 to present	None
Language	English language only	None
Countries	No limit	None
Key: CAH, congenital adrenal hyperplasia; SLR, systematic literature review. **Notes:** [a], systematic reviews were included and flagged for bibliography searches		

Systematic literature review of utility and HRQL studies

The inclusion and exclusion criteria for utility studies are specified in Table 91 in terms of population, interventions, comparators, outcomes, study type and others.

Category	Inclusion criteria	Exclusion criteria
Population	Adults and adolescents (age ≥12 years) patients with CAH	• Healthy volunteers • Patient population without CAH Patients with non-classical CAH
Interventions	No limit	None
Comparators	No limit	None
Outcomes	• All types of utilities data including EQ-5D, SF-6D, etc. • Health state utility data, disutilities, etc. • Sources of utility and disutility	Studies not reporting utility values/HRQL (SF-36/EQ-5D)
Study type	Studies reporting • QoL data • Utility data	• Letters, comment, and editorials • Case reports
Time limit	No restrictions	None
Language	English language only	None
Countries	No limit	None
Key: CAH, congenital adrenal hyperplasia; QoL, quality of life; SF-6D, Short-Form Six-Dimensions utility index; SLR, systematic literature review. **Notes:** [a], systematic reviews were included and flagged for bibliography searches;		

Appendix I Mapping of HRQoL data

Not applicable – mapping of HRQoL data was not conducted.

Appendix J Probabilistic sensitivity analyses

Summary of probabilistic sensitivity analyses is provided in the table below. Please see sheet called PSA in the excel Efmody cost-effectiveness model for further information.

Technology	Costs	LYs	QALYs	Incremental Costs	Incremental LYs	Incremental QALYs	ICER (kr./QALY)
Deterministic results							
Standard care	1,020,428 kr.	22.45	16.72				
Efmody	1,292,522 kr.	24.75	20.29	272,094 kr.	2.290505448	3.567244863	76,276
Probabilistic results							
Standard care	1,231,235 kr.	22.43	16.66				
Efmody	1,498,011 kr.	24.52	19.84	266,775 kr.	2.087348999	3.181319159	83,857

Appendix K Product cost information

Table 92: AIP prices – Efmody and glucocorticoids available in Denmark (medicinpriser.dk Sep 8, 2021)

Efmody - AIP per pack (5 mg, 10 mg)	**Efmody - AIP per mg**
1,125.56 (50 pack)	4.50
2,251.11 (50 pack)	4.50
Hydrocortisone Orion tablets - AIP per pack (10 mg)	**Hydrocortisone Orion tablets - AIP per mg**
34.63 (30 pack)	0.12
81.00 (100 pack)	0.08
Hydrocortisone Takeda tablets - AIP per pack (20 mg)	**Hydrocortisone Takeda tablets - AIP per mg**
139.47 (100 pack)	0.07
Alkindi - AIP per pack (1 mg, 50)	**Alkindi – AIP per mg**
663.8 (50 pack)	13,28
Plenadren Orion - AIP per pack (5 mg, 20 mg)	**Plenadren Orion - AIP per mg**
1,789.72 (50 pack)	7.16
Plenadren Takeda - AIP per pack (5 mg, 20 mg)	**Plenadren Takeda - AIP per mg**
1,804.31 (50 pack)	7.22

3,610.81 (50 pack)	3.61
Plenadren Abacus - AIP per pack (5 mg, 20 mg)	**Plenadren Abacus - AIP per mg**
1,780.72 (50 pack)	7.12
Prednisolone DAK - AIP per pack (5 mg)	**Prednisolone DAK - AIP per mg**
38.43 (100 pack)	0.08

Drug acquisition cost per mg in PPP for the comparators used for modeling are presented in Table 93.

Table 93: Primary model costs (PPP): Drug acquisition costs and current percentage usage of SOC (all medications)

CAH medication (Adults)						
Treatment	**Average cost per mg (DKK)**	**Unit dose (mg)**	**Daily dose (mg)**	**Cost per one month cycle (DKK)**	**Percentage usage**	**Source**
Hydrocortisone	0.10	10	30	72.35	77%	MEDICINPRISER.DK - 2021/9/08
	0.07	20				
Plenadren	7.17	5	30	4,379.33	20%	
	3.61	20				
Prednisolone	0.08	5	5	11.69	3%	
CAH medication (Adolescents)						
Treatment	**Average cost per mg (DKK)**	**Unit dose (mg)**	**Daily dose (mg)**	**Cost per one month cycle (DKK)**	**Percentage usage**	**Source**
Hydrocortisone	0.10	10	15	44.84	82.00%	MEDICINPRISER.DK - 2021/9/08
	0.07	20				
Prednisolone	0.08	5	5	5.85	3%	
Alkindi	13.28	1, 2 or 5	15	822.57*	15.00%	

Table 5. Prices of Glucocorticoids Available in Denmark (medicinpriser.dk, Sept 10, 2021)

Medicinal product	Strength	Package	Active substance	Company	ATC code	Pharmacy purchase price (AIP)	Price per DDD	Reimbursement calculated from	Price per unit	Pharmacy retail price
Alkindi 497083	1 mg	50 stk. granulat, enkeltdos.	Hydrocortison	FrostPharma	H02AB09	663.80	545,68	909.65	18.19	909.65
Alkindi 467473	2 mg	50 stk. granulat,	Hydrocortison	FrostPharma	H02AB09	1,327.59	540,79	1,802.45	36.05	1,802.45

		enkeltdos.								
Alkindi 582671	5 mg	50 stk. granulat, enkeltdos.	Hydrocortison	FrostPharma	H02AB09	3,318.98	537.72	4,480.85	89.62	4,480.85
Hydrokortison "Orion" 49319	10 mg	30 stk. (blister) tabletter	Hydrocortison	Orion Pharma	H02AB09	34.63	6.34	63.40	2.11	63.40
Hydrokortison "Orion" 487361	10 mg	100 stk. (blister) tabletter	Hydrocortison	Orion Pharma	H02AB09	81.00	3.77	125.75	1.26	125.75
Hydrokortison "TAKEDA" 490667	20 mg	100 stk. tabletter	Hydrocortison	Takeda Pharma	H02AB09	139.47	3.02	204.40	2.02	204.40
Plenadren 128507	5 mg	50 stk. (Orifarm) tabl. m modif udlø ...	Hydrocortison	Orifarm	H02AB09	1,789.72	290.89	2,424.00	48.48	2,424.00
Plenadren 155579	5 mg	50 stk. tabl. m modif udløsn	Hydrocortison	Takeda Pharma	H02AB09	1,804.31	293.24	2,443.60	48.87	2,443.60
Plenadren 174350	5 mg	50 stk. (Abacus) tabl. m modif udløs ...	Hydrocortison	Abacus	H02AB09	1,780.72	292.87	2,411.9	48.81	2,440.50
Plenadren 424199	20 mg	50 stk. tabl. m modif udløsn	Hydrocortison	Takeda Pharma	H02AB09	3,610.81	146.20	4,873.35	97.47	4,873.35
Prednisolon "DAK" 398747	5 mg	100 stk. tabletter	Prednisolon	Takeda Pharma	H02AB06	38.43	1,37	68.50	0.69	68.50
Dexametason "Abcur" 39413	1 mg	20 stk. (unit-dose) tabletter	Dexamethason	Abcur AB	H02AB02	133	14.68	195.70	9.79	195.70
Dexametason "Abcur" 126955	1 mg	100 stk. (unit-dose)	Dexamethason	Abcur AB	H02AB02	523	10.80	720.25	7.20	720.25

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		tablett er								

Appendix L Alkindi TLV submission – economic analysis [redacted]

Alkindi TLV submission_economi

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