

**Clinical trial results:****Optimizing timing of glucocorticoid treatment in children with congenital adrenal hyperplasia****Summary**

EudraCT number	2018-004802-24
Trial protocol	NL
Global end of trial date	14 June 2020

Results information

Result version number	v1 (current)
This version publication date	04 August 2022
First version publication date	04 August 2022
Summary attachment (see zip file)	Manuscript OPTIMED JCEM (dgab826_manuscript_optimed.pdf)

Trial information**Trial identification**

Sponsor protocol code	NL68556.091.18
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Innovatiefonds zorgverzekeraars
Sponsor organisation address	NA, NA, Netherlands, NA
Public contact	Department of Ped Endocrinology, Radboud University Nijmegen medical centre, +31 243614430, hedi.claahsen@radboudumc.nl
Scientific contact	Department of Ped Endocrinology, Radboud University Nijmegen medical centre, +31 243614430, hedi.claahsen@radboudumc.nl

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 June 2020
Global end of trial reached?	Yes
Global end of trial date	14 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To study the effects of 2 standard treatment timing strategies for glucocorticoid dosage on androgen concentration in CAH children: a. highest dosage in the morning, b. highest dosage in the evening.

Protection of trial subjects:

NA

Background therapy:

NA

Evidence for comparator:

NA

Actual start date of recruitment	01 January 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 41
Worldwide total number of subjects	41
EEA total number of subjects	41

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	16
Adolescents (12-17 years)	20
Adults (18-64 years)	5
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were actively recruited via BijnierNet and their pediatric endocrinologists in The Netherlands. By completing a contact form, patients and parents could indicate their interest in the study and provided consent to be contacted by the study coordinator.

Pre-assignment

Screening details:

Inclusion:

- Classic 21OHD
- Diagnosis confirmed by hormonal and mutation analysis
- 4 -20 yrs.
- Treatment with Hydrocortisone.
- Ability to collect saliva

Exclusion:

Chronic medication use other than hydrocortisone or fludrocortisone

1 patient was excluded due to medication use. Two patients withdrew informed consent.

Period 1

Period 1 title	Intervention cross-over study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
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Arm title	Highest dosage morning
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Arm description:

Patient received highest hydrocortisone dose in the morning

Arm type	Active comparator
Investigational medicinal product name	Hydrocortisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patient administered their own formulation of hydrocortisone and patients continued their regular dosage, either administering the highest dosage in the morning or in the evening.

Arm title	Highest dose evening
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Arm description:

Patient received the highest hydrocortisone dose in the evening.

Arm type	Active comparator
Investigational medicinal product name	Hydrocortisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patient administered their own formulation of hydrocortisone and patients continued their regular dosage, either administering the highest dosage in the morning or in the evening.

Number of subjects in period 1	Highest dosage morning	Highest dose evening
Started	39	40
Completed	39	40

Baseline characteristics

Reporting groups

Reporting group title	Intervention cross-over study
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Reporting group description:

39 patients completed the six-week cross-over study comparing the administration of the highest dose of hydrocortisone in the morning (3 weeks) with the administration of hydrocortisone in the evening (3 weeks). Patients used their regular hydrocortisone medication and started the first three-week period of the study with their regular dosing regimen. After three weeks patients switched to the other hydrocortisone dose timing regimen.

Reporting group values	Intervention cross-over study	Total	
Number of subjects	41	41	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	16	16	
Adolescents (12-17 years)	20	20	
Adults (18-64 years)	5	5	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
median	12		
full range (min-max)	4 to 19	-	
Gender categorical			
Units: Subjects			
Female	19	19	
Male	22	22	

End points

End points reporting groups

Reporting group title	Highest dosage morning
Reporting group description: Patient received highest hydrocortisone dose in the morning	
Reporting group title	Highest dose evening
Reporting group description: Patient received the highest hydrocortisone dose in the evening.	

Primary: 17-hydroxyprogesterone

End point title	17-hydroxyprogesterone ^[1]
End point description:	
End point type	Primary
End point timeframe: 17-hydroxyprogesterone levels were reported at 5.00AM, 7.00AM, 3.00PM, 11.00PM at day 20 and 21 of 41 and 42 of the intervention period.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: A detailed description of the statistical analyses can be found in the manuscript: DOI: 10.1210/clinem/dgab826

End point values	Highest dosage morning	Highest dose evening		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: nmol/L				
median (inter-quartile range (Q1-Q3))				
5.00AM	0.566 (0.204 to 1.252)	0.250 (0.045 to 0.745)		
7.00AM	1.357 (0.537 to 3.814)	1.909 (0.738 to 2.753)		
3.00PM	0.518 (0.084 to 1.748)	0.786 (0.424 to 2.045)		
11.00PM	0.078 (0.024 to 0.167)	0.100 (0.040 to 0.164)		

Statistical analyses

No statistical analyses for this end point

Primary: androstenedione

End point title	androstenedione ^[2]
End point description:	
End point type	Primary

End point timeframe:

Androstenedione was quantified in saliva collected at 5.00AM, 7.00AM, 3.00PM, and 11.00PM.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: A detailed description of the statistical analyses can be found in the manuscript: DOI: 10.1210/clinem/dgab826

End point values	Highest dosage morning	Highest dose evening		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: nmol/L				
median (inter-quartile range (Q1-Q3))				
5.00AM	0.162 (0.062 to 0.418)	0.188 (0.058 to 0.341)		
7.00AM	0.232 (0.100 to 0.689)	0.381 (0.165 to 0.701)		
3.00PM	0.121 (0.055 to 0.352)	0.281 (0.088 to 0.469)		
11.00PM	0.065 (0.022 to 0.198)	0.096 (0.031 to 0.252)		

Statistical analyses

No statistical analyses for this end point

Secondary: Subjective sleepscores

End point title Subjective sleepscores

End point description:

End point type Secondary

End point timeframe:

Patients (or their caretakers) gave daily sleepscores during the entire study period.

End point values	Highest dosage morning	Highest dose evening		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: 1-5	5	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Subjective activity scores

End point title Subjective activity scores

End point description:

Mean of mean sleepscores per subject are provided.

End point type Secondary

End point timeframe:

Patients (or their caretakers) gave daily activity scores during the entire study period.

End point values	Highest dosage morning	Highest dose evening		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: 1-10				
Morning	6	6		
Afternoon	7	7		
Evening	6	6		

Statistical analyses

No statistical analyses for this end point

Secondary: Blood pressure

End point title Blood pressure

End point description:

End point type Secondary

End point timeframe:

Overnight blood pressure was determined for 1 night during week 3 and week 6 of the intervention period.

End point values	Highest dosage morning	Highest dose evening		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	30		
Units: mmHg				
arithmetic mean (full range (min-max))				
Systolic	108.8 (94.6 to 125.6)	106.5 (84.4 to 127.9)		
Diastolic	61.8 (45.7 to 73.0)	60.5 (49.7 to 71.75)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Start study intervention until the end of intervention.

Adverse event reporting additional description:

Patients were asked to write down adverse events in a diary or by contacting the study team.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	5
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Reporting groups

Reporting group title	Subjects participating intervention period
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Reporting group description: -

Serious adverse events	Subjects participating intervention period		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 39 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Subjects participating intervention period		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 39 (28.21%)		
General disorders and administration site conditions			
General malaise	Additional description: Not related to hydrocortisone.		
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Stomach ache	Additional description: One time not related to hydrocortisone and one time not known if related to hydrocortisone.		
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Inflammation perineum	Additional description: Not related to hydrocortisone.		

subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1		
Stomach ache/vomitting	Additional description: Not related to hydrocortisone.		
subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1		
Headache	Additional description: Not known if related to hydrocortisone.		
subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1		
Illness	Additional description: Not related to hydrocortisone.		
subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Cold sore	Additional description: Not related to hydrocortisone.		
subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1		
Falling off the stairs			
subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1		
Common cold	Additional description: Not related to hydrocortisone.		
subjects affected / exposed occurrences (all)	1 / 39 (2.56%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 July 2019	The inclusion criteria on age was adapted from 4-18 years to children from 4 years of age and adolescents.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

NA

Notes: