Clinical trial results:
PlenadrEMA study - Effect of modified-release compared to conventional hydrocortisone on fatigue, measured by Ecological Momentary Assessments; a pilot study to assess feasibility, responsiveness of outcomes and to inform power calculations for future large-scale RCTs

Summary

EudraCT number	2014-002039-32
Trial protocol	DK
Global end of trial date	03 June 2019

Results information

Result version number	v1 (current)
This version publication date	21 March 2021
First version publication date	21 March 2021
Summary attachment (see zip file)	Summary (summary til results EudraCT.docx)

Trial information

Trial identification

Sponsor protocol code	PlenadrEMA/1.1/2014

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Copenhagen University Hospital, Rigshospitalet
Sponsor organisation address	Blegdamsvej 9, Copenhagen, Denmark, 2100
Public contact	PlenadrEMA Study Information, Copenhagen University Hospital, Rigshospitalet, +45 35452535, thea.christoffersen@regionh.dk
Scientific contact	PlenadrEMA Study Information, Copenhagen University Hospital, Rigshospitalet, +45 35452535, thea.christoffersen@regionh.dk

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	24 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 June 2019
Global end of trial reached?	Yes
Global end of trial date	03 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate feasibility of EMA assessments as outcome in future large-scale randomized clinical trials (RCT) of modified release hydrocortisone.
To quantify the variability of such measurements in patients with adrenal insufficiency due to hypopituitarism and to acquire an estimate of the size of the expected difference in scores; both of which are required for sample size calculations.
To identify the best suited outcome for an RCT, i.e. the most informative with the least participant burden; i.e. the most responsive, brief summary measure.

Protection of trial subjects:

Patients kept a diary to register disease, stress or other events. They were instructed to administer supplementary hydrocortisone in these instances.
Blood samples were drawn at screening, baseline and follow-up to make sure trial subjects' biochemistry were in order.

Background therapy:

Patients continued their standard care as per clinical guidelines in the first phase of the trial which was the comparator
For the second part of the trial, all participant switched to the imp

Evidence for comparator:

The comparator in this study was hydrocortisone. In this patient population, hydrocortisone is vital and standard treatment.

Actual start date of recruitment	01 April 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 31
Worldwide total number of subjects	31
EEA total number of subjects	31

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	17
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from the outpatient clinic at the department of Endocrinology and Metabolism, Rigshospitalet,
Copenhagen University Hospital.
Recruitment took place from March 2018 to January 2019

Pre-assignment

Screening details:

From March 2018 to January 2019, patients receiving hydrocortisone tablets from the outpatient clinic at the Department of Endocrinology and Metabolism, Rigshospitalet, were screened for eligibility.

Period 1

Period 1 title	baseline period - comparator
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

n/a

Arms

Arm title	Comparator

Arm description:

Standard hydrocortisone replacement therapy

Arm type	Active comparator
Investigational medicinal product name	hydrocortisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

As per routine clinical care

Number of subjects in period 1	Comparator
Started	31
Completed	31

Period 2

Period 2 title	follow up - imp
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

n/a

Arms

Arm title	follow up - imp

Arm description:

All participants were switched to imp

Arm type	Experimental
Investigational medicinal product name	plenadren
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received the same total daily dose as on conventional hydrocortisone and were instructed to take the dose in fasting state upon waking. Plenadren is only available in 20 and 5 mg tablets; consequently, intermediate doses were rounded up to the nearest 5 mg (e.g., three-times daily hydrocortisone: 10 + 5 + 2.5 mg was transformed to 20 mg of Plenadren).

Number of subjects in period 2	follow up - imp
Started	31
Completed	27
Not completed	4
Consent withdrawn by subject	1
Adverse event, non-fatal	3

Baseline characteristics

Reporting groups	
Reporting group title	baseline period - comparator
Reporting group description:	
Patients with secondary adrenal insuficiency due to hypopituitarism	

Reporting group values	baseline period - comparator	Total	
Number of subjects	31	31	
Age categorical Units: Subjects			
Adults (18-64 years)	17	17	
From 65-84 years	14	14	
Age continuous Units: years median full range (min-max)	 61 38 to 76	 -	
Gender categorical Units: Subjects			
Female	4	4	
Male	27	27	
MFI20 - general fatigue			
MFI20 - general fatigue			
Units: score arithmetic mean standard deviation	 10.3 ± 4.5	 -	
MFI20 - reduced motivation			
MFI20 - reduced motivation			
Units: score arithmetic mean standard deviation	 8.8 ± 4.0	 -	
MFI20 - physical fatigue			
MFI20 - physical fatigue			
Units: score arithmetic mean standard deviation	 9.5 ± 4.3	 -	
MFI20 - reduced activity			
MFI20 - reduced activity			
Units: score arithmetic mean standard deviation	 9.1 ± 4.25	 -	
MFI20 - mental fatigue			
MFI20 - mental fatigue			
Units: score arithmetic mean standard deviation	 8.9 ± 14.7	 -	

End points

End points reporting groups	
Reporting group title	Comparator
Reporting group description: Standard hydrocortisone replacement therapy	
Reporting group title	follow up - imp
Reporting group description: All participants were switched to imp	

Primary: MFI20 - general fatigue	
End point title	MFI20 - general fatigue
End point description:	
End point type	Primary
End point timeframe: After 16 weeks of imp	

End point values	Comparator	follow up - imp		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: score				
arithmetic mean (standard deviation)	10.3 (± 4.5)	9.3 (± 4.6)		

Statistical analyses

Statistical analysis title	mixed models for repeated measurements
Comparison groups	Comparator v follow up - imp
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.37
Variability estimate	Standard error of the mean
Dispersion value	0.16

Primary: MFI20 - reduced motivation	
End point title	MFI20 - reduced motivation
End point description:	
End point type	Primary
End point timeframe: after 16 weeks of imp	

End point values	Comparator	follow up - imp		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: score				
arithmetic mean (standard deviation)	8.8 (± 4.0)	9.3 (± 4.6)		

Statistical analyses

Statistical analysis title	mixed models for repeated measurements
Comparison groups	Comparator v follow up - imp
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	1.45
Variability estimate	Standard error of the mean
Dispersion value	0.3

Primary: MFI20 - physical fatigue	
End point title	MFI20 - physical fatigue
End point description:	
End point type	Primary
End point timeframe: after 16 weeks of imp	

End point values	Comparator	follow up - imp		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: score				
arithmetic mean (standard deviation)	9.5 (± 4.3)	8.6 (± 4.4)		

Statistical analyses

Statistical analysis title	mixed models for repeated measurements
Comparison groups	follow up - imp v Comparator
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.43
Variability estimate	Standard error of the mean
Dispersion value	0.26

Primary: MFI20 - reduced activity

End point title	MFI20 - reduced activity
End point description:	
End point type	Primary
End point timeframe: after 16 weeks on IMP	

End point values	Comparator	follow up - imp		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: score				
arithmetic mean (standard deviation)	9.1 (± 4.3)	13.2 (± 4.5)		

Statistical analyses

Statistical analysis title	mixed models for repeated measurements
Comparison groups	Comparator v follow up - imp
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	0.29

Primary: MFI20 - mental fatigue	
End point title	MFI20 - mental fatigue
End point description:	
End point type	Primary
End point timeframe: after 16 weeks on IMP	

End point values	Comparator	follow up - imp		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: score				
arithmetic mean (standard deviation)	8.9 (± 3.8)	8.2 (± 3.7)		

Statistical analyses

Statistical analysis title	mixed models for repeated measurements
Comparison groups	Comparator v follow up - imp

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	0.17

Adverse events

Adverse events information

Timeframe for reporting adverse events:

21 weeks:
5 weeks on comparator and 16 weeks for imp.

Adverse event reporting additional description:

through diary.
And at all visits, patients were asked about AEs

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	comparator

Reporting group description: -

Reporting group title	follow-up - imp

Reporting group description: -

Serious adverse events	comparator	follow-up - imp	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 31 (0.00%)	3 / 31 (9.68%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pituitary adenoma enlargement	Additional description: Pituitary adenoma enlargement		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrilation	Additional description: Patient with paroxysmal atrial fibrilation had an electrical cardioversion performed twice due to exacerbations		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dilated cardiomyopathy	Additional description: Hospitalization where patient was diagnosed with dilated cardiomyopathy		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 31 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	comparator	follow-up - imp	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 31 (16.13%)	18 / 31 (58.06%)	
Nervous system disorders			
Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 31 (0.00%)	6 / 31 (19.35%)	
occurrences (all)	0	6	
Skin and subcutaneous tissue disorders			
Rash			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Photosensitivity reaction			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 31 (0.00%)	2 / 31 (6.45%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Myalgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 31 (3.23%)	1 / 31 (3.23%)	
occurrences (all)	1	1	
Infections and infestations			
Nasopharyngitis			
alternative assessment type: Non-systematic			

subjects affected / exposed	3 / 31 (9.68%)	4 / 31 (12.90%)	
occurrences (all)	3	4	
Pneumonia			
subjects affected / exposed	1 / 31 (3.23%)	1 / 31 (3.23%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported