Clinical trial results:
A randomized double blind cross-over study of the effects of low dose and high dose hydrocortisone replacement therapy on cognition, quality of life, metabolic profile and somatosensation in patients with secondary adrenal insufficiency

Summary

EudraCT number	2011-000864-82
Trial protocol	NL
Global end of trial date	12 June 2013
Results information	
Result version number	v1 (current)
This version publication date	16 February 2016
First version publication date	26 June 2014

Trial information

Trial identification	
Sponsor protocol code	hydrocortisone
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01546922
WHO universal trial number (UTN)	-
Other trial identifiers	ABR : 35668

Notes:

Sponsors	
Sponsor organisation name	University Medical Center Groningen
Sponsor organisation address	Department of Endocrinology, AA31, Postbus 30.001, GRONINGEN, Netherlands, 9700 RB
Public contact	Department of Endocrinology, University Medical Center Groningen, +31 503613962, n.alma@umcg.nl
Scientific contact	Department of Endocrinology, University Medical Center Groningen, +31 503613962, n.alma@umcg.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	30 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 June 2013
Global end of trial reached?	Yes
Global end of trial date	12 June 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this study is to investigate whether a physiologically low HC dose is better for cognition as compared to a high HC dose.

Protection of trial subjects:

Additional hydrocortisone escape medication to provide an imitation of a physiological stress response is allowed. The pharmacy of the UMCG was able to break the randomisation code in case of experienced serious discomfort in the patients' physical or mental functioning caused by the new hydrocortisone dose. Adverse events were assessed systematically during the scheduled visits to the hospital and halfway during a treatment period.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 January 2012
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: 63
Worldwide total number of subjects	63
EEA total number of subjects	63

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)	55
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 63 patients were included. Patients on cortisone acetate were converted to hydrocortisone in a bioequivalent dose during the run-in phase. Three patients withdrew during the run-in phase, therefore a total of 60 patients started the treatment periods.

Period 1

Period 1 title	First period of ten weeks
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	First a low dose HC followed by a high dose HC

Arm description:

In this arm patients first received a low dose of hydrocortisone for ten weeks followed by a high dose of hydrocortisone for ten weeks.

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:

Patients received 0.2-0.3 mg hydrocortisone per kg body weight

Arm title	First a high dose HC followed by a low dose HC

Arm description:

In this arm patients first received a high dose of hydrocortisone for ten weeks followed by a low dose of hydrocortisone for ten weeks

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:

Patients received 0.4-0.6 mg hydrocortisone per kg body weight

Number of subjects in period 1	First a low dose HC followed by a high dose HC	First a high dose HC followed by a low dose HC
Started	30	30
Completed	25	28
Not completed	5	2
Consent withdrawn by subject	1	1
Broken arm, investigators judgement	1	-
Protocol deviation	3	1

Period 2

Period 2 title	Second period of ten weeks
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	First a low dose HC followed by a high dose HC

Arm description:

In this arm patients first received a low dose of hydrocortisone for ten weeks followed by a high dose of hydrocortisone for ten weeks.

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:

Patients received 0.4-0.6 mg hydrocortisone per kg body weight

Arm title	First a high dose HC followed by a low dose HC

Arm description:

In this arm patients first received a high dose of hydrocortisone for ten weeks followed by a low dose of hydrocortisone for ten weeks

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:

Patients received 0.2-0.3 mg hydrocortisone per kg body weight

Number of subjects in period 2	First a low dose HC followed by a high dose HC	First a high dose HC followed by a low dose HC
Started	25	28
Completed	22	25
Not completed	3	3
Consent withdrawn by subject	-	2
Protocol deviation	3	1

Period 3	
Period 3 title	Completed both study periods
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	No
Arm title	Subjects receiving a low dose of hydrocortisone
Arm description: -	
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: Patients received 0.2-0.3 mg hydrocortisone per kg body weight	
Arm title	Subject receiving a high dose of hydrocortisone
Arm description: -	
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: Patients received 0.4-0.6 mg hydrocortisone per kg body weight	

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline characteristics are based on the 47 patients that completed both study periods.

Number of subjects in period 3	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone
Started	47	47
Completed	47	47

Baseline characteristics

Reporting groups[1]	
Reporting group title	Completed both study periods
Reporting group description: -	

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on the 47 patients that completed both study periods.

Reporting group values	Completed both study periods	Total	
Number of subjects	47	47	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	55		
inter-quartile range (Q1-Q3)	43 to 61	-	
Gender categorical Units: Subjects			
Female	18	18	
Male	29	29	
Childhood onset / Adult onset Units: Subjects			
Childhood onset	6	6	
Adult onset	41	41	
Type of surgery Units: Subjects			
Transsphenoïdal surgery	23	23	
Craniotomy	9	9	
No surgery	15	15	
Patients with a second surgery Units: Subjects			
Second surgery	5	5	
No second surgery	42	42	
Type of radiotherapy Units: Subjects			
Pituitary radiotherapy	16	16	
Cranial irradiation	2	2	

Radiotherapy for extracranial tumors	1	1	
No radiotherapy	28	28	
Number of daily dosings prior to randomization			
Units: Subjects			
1 dose per day	3	3	
2 doses per day	33	33	
3 doses per day	11	11	
Number of hormonal replacements			
Units: Subjects			
1 hormonal replacement	3	3	
2 hormonal replacements	9	9	
3 hormonal replacements	21	21	
4 hormonal replacements	11	11	
5 hormonal replacements	3	3	
Thyroid hormone			
Units: Subjects			
Substituted	43	43	
Unsubstituted	4	4	
Growth hormone			
Units: Subjects			
Substituted	21	21	
Unsubstituted - growth hormone deficiency	10	10	
Unsubstituted - no growth hormone deficiency	16	16	
Sex hormone			
Units: Subjects			
Men: testosterone	23	23	
Premenopausal women: estrogen	4	4	
Unsubstituted	20	20	
Desmopressin substitution			
Units: Subjects			
Substituted	9	9	
Unsubstituted	38	38	
Age at diagnosis			
Units: years			
median	31		
inter-quartile range (Q1-Q3)	20 to 46	-	
Body weight			
Units: kg			
median	82.5		
inter-quartile range (Q1-Q3)	72.2 to 93	-	
Age at surgery			
Units: years			
median	39		
inter-quartile range (Q1-Q3)	28 to 50	-	
Time since surgery			
Units: years			
median	11		
inter-quartile range (Q1-Q3)	6 to 20	-	
Age at radiotherapy			

Units: years			
median	43		
inter-quartile range (Q1-Q3)	25 to 52	-	
Time since radiotherapy			
Units: years			
median	12		
inter-quartile range (Q1-Q3)	9 to 22	-	
Total daily dose hydrocortisone treatment prior to randomization			
Units: mg/day			
median	25		
inter-quartile range (Q1-Q3)	20 to 30	-	
Dose per kg body weight prior to randomization			
Units: mg/kg body weight			
median	0.32		
inter-quartile range (Q1-Q3)	0.25 to 0.35	-	
Duration of hydrocortisone treatment prior to randomization			
Units: years			
median	12		
inter-quartile range (Q1-Q3)	5 to 22	-	

End points

End points reporting groups

Reporting group title	First a low dose HC followed by a high dose HC
Reporting group description:	
In this arm patients first received a low dose of hydrocortisone for ten weeks followed by a high dose of hydrocortisone for ten weeks.	
Reporting group title	First a high dose HC followed by a low dose HC
Reporting group description:	
In this arm patients first received a high dose of hydrocortisone for ten weeks followed by a low dose of hydrocortisone for ten weeks	
Reporting group title	First a low dose HC followed by a high dose HC
Reporting group description:	
In this arm patients first received a low dose of hydrocortisone for ten weeks followed by a high dose of hydrocortisone for ten weeks.	
Reporting group title	First a high dose HC followed by a low dose HC
Reporting group description:	
In this arm patients first received a high dose of hydrocortisone for ten weeks followed by a low dose of hydrocortisone for ten weeks	
Reporting group title	Subjects receiving a low dose of hydrocortisone
Reporting group description: -	
Reporting group title	Subject receiving a high dose of hydrocortisone
Reporting group description: -	

Primary: RBMT - immediate memory

End point title	RBMT - immediate memory
End point description:	
End point type	Primary
End point timeframe:	
Cognitive performance was measured after each treatment period.	

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	-0.41 (± 0.95)	-0.42 (± 1.33)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC

Statistical analysis description:	
Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone	
Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.861 [1]
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: RBMT - delayed memory

End point title	RBMT - delayed memory
End point description:	
End point type	Primary
End point timeframe:	
Cognitive performance was measured after each treatment period.	

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	0.07 (± 0.98)	0.1 (± 1.33)		

Statistical analyses

Statistical analysis title	Low dose versus high dose
Statistical analysis description:	
Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone	
Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.668 [2]
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: RBMT - delayed corrected for immediate memory

End point title	RBMT - delayed corrected for immediate memory

End point description:

End point type	Primary

End point timeframe:

Cognitive performance was measured after each treatment period.

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	0.85 (± 1.09)	0.89 (± 1.34)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC

Statistical analysis description:

Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.

Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.713 [3]
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: 15 Words Test - Short-term memory

End point title	15 Words Test - Short-term memory

End point description:

End point type	Primary

End point timeframe:

Cognitive performance was measured after each treatment period.

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	0.36 (± 1.01)	-0.03 (± 1.03)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC

Statistical analysis description:

Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.

Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.028 [4]
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: 15 Words Test - Total immediate memory

End point title	15 Words Test - Total immediate memory

End point description:

End point type	Primary

End point timeframe:

Cognitive performance was measured after each treatment period.

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	0.43 (± 1.02)	0.25 (± 0.92)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC

Statistical analysis description:	
Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.	
Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.227 [5]
Method	Wilcoxon (Mann-Whitney)

Notes:

[5] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: 15 Words Test - Learning score

End point title	15 Words Test - Learning score
End point description:	
End point type	Primary
End point timeframe:	
Cognitive performance was measured after each treatment period.	

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	0.08 (± 1.05)	0.38 (± 1.19)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC
Statistical analysis description:	
Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.	
Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.13 [6]
Method	Wilcoxon (Mann-Whitney)

Notes:

[6] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: 15 Words Test - Delayed memory

End point title	15 Words Test - Delayed memory

End point description:

End point type	Primary

End point timeframe:

Cognitive performance was measured after each treatment period.

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	0.02 (± 1.04)	0.23 (± 0.97)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC

Statistical analysis description:

Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.

Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.106 [7]
Method	Wilcoxon (Mann-Whitney)

Notes:

[7] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: 15 Words Test - Delayed corrected for total memory

End point title	15 Words Test - Delayed corrected for total memory

End point description:

End point type	Primary

End point timeframe:

Cognitive performance was measured after each treatment period.

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	-0.3 (± 0.99)	-0.16 (± 0.99)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC

Statistical analysis description:

Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.

Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.35 [8]
Method	Wilcoxon (Mann-Whitney)

Notes:

[8] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: 15 Words Test - Recognition

End point title	15 Words Test - Recognition

End point description:

End point type	Primary

End point timeframe:

Cognitive performance was measured after each treatment period.

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	-0.11 (± 0.88)	0.08 (± 0.71)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC

Statistical analysis description:	
Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.	
Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.093 [9]
Method	Wilcoxon (Mann-Whitney)

Notes:

[9] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: Digit Span forward

End point title	Digit Span forward
End point description:	
End point type	Primary
End point timeframe:	
Cognitive performance was measured after each treatment period.	

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	0.49 (± 0.97)	0.56 (± 0.97)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC
Statistical analysis description:	
Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.	
Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.614 [10]
Method	Wilcoxon (Mann-Whitney)

Notes:

[10] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: Rey Complex Figure - Immediate memory

End point title	Rey Complex Figure - Immediate memory

End point description:

End point type	Primary

End point timeframe:

Cognitive performance was measured after each treatment period.

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	1.14 (± 1.26)	1.4 (± 1.29)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC

Statistical analysis description:

Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.

Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.111 [11]
Method	Wilcoxon (Mann-Whitney)

Notes:

[11] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: Rey Complex Figure - delayed memory

End point title	Rey Complex Figure - delayed memory

End point description:

End point type	Primary

End point timeframe:

Cognitive performance was measured after each treatment period.

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	1.11 (± 1.22)	1.28 (± 1.29)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC

Statistical analysis description:

Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.

Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.451 [12]
Method	Wilcoxon (Mann-Whitney)

Notes:

[12] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: Divided attention - reaction time auditory responses

End point title	Divided attention - reaction time auditory responses

End point description:

End point type	Primary

End point timeframe:

Cognitive performance was measured after each treatment period.

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	-0.87 (± 0.81)	-0.89 (± 0.82)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC

Statistical analysis description:	
Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.	
Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.905 [13]
Method	Wilcoxon (Mann-Whitney)

Notes:

[13] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: Divided attention - reaction time visual response

End point title	Divided attention - reaction time visual response
End point description:	
End point type	Primary
End point timeframe:	
Cognitive performance was measured after each treatment period.	

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	-0.06 (± 1)	0.03 (± 0.94)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC
Statistical analysis description:	
Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.	
Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.502 [14]
Method	Wilcoxon (Mann-Whitney)

Notes:

[14] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: Divided attention - Number of omission errors

End point title	Divided attention - Number of omission errors

End point description:

End point type	Primary

End point timeframe:

Cognitive performance was measured after each treatment period.

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	-0.02 (± 0.86)	-0.14 (± 0.93)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC

Statistical analysis description:

Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.

Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.531 [15]
Method	Wilcoxon (Mann-Whitney)

Notes:

[15] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: Divided attention - Number of commission errors

End point title	Divided attention - Number of commission errors

End point description:

End point type	Primary

End point timeframe:

Cognitive performance was measured after each treatment period.

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	0.3 (± 1.01)	0.34 (± 0.76)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC

Statistical analysis description:

Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.

Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.681 [16]
Method	Wilcoxon (Mann-Whitney)

Notes:

[16] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: Visual scanning - reaction time for target stimuli

End point title	Visual scanning - reaction time for target stimuli

End point description:

End point type	Primary

End point timeframe:

Cognitive performance was measured after each treatment period.

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	-0.38 (± 1.04)	-0.36 (± 1.03)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC

Statistical analysis description:	
Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.	
Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.713 [17]
Method	Wilcoxon (Mann-Whitney)

Notes:

[17] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: Visual scanning - Number of omission errors

End point title	Visual scanning - Number of omission errors

End point description:

End point type	Primary

End point timeframe:

Cognitive performance was measured after each treatment period.

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	-0.03 (± 1.06)	0.08 (± 1.08)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC

Statistical analysis description:

Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.

Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.229 [18]
Method	Wilcoxon (Mann-Whitney)

Notes:

[18] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: Visual scanning - Number of commission errors

End point title	Visual scanning - Number of commission errors

End point description:

End point type	Primary

End point timeframe:

Cognitive performance was measured after each treatment period.

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	-0.72 (± 0.26)	-0.7 (± 0.28)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC

Statistical analysis description:

Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.

Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.329 [19]
Method	Wilcoxon (Mann-Whitney)

Notes:

[19] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: Alertness - Reaction time tonic alertness

End point title	Alertness - Reaction time tonic alertness

End point description:

End point type	Primary

End point timeframe:

Cognitive performance was measured after each treatment period.

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	-0.9 (± 0.73)	-0.99 (± 0.73)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC

Statistical analysis description:

Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.

Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.192 [20]
Method	Wilcoxon (Mann-Whitney)

Notes:

[20] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: Alertness - Reaction time phasic alertness

End point title	Alertness - Reaction time phasic alertness

End point description:

End point type	Primary

End point timeframe:

Cognitive performance was measured after each treatment period.

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	-1.03 (± 0.67)	-1.1 (± 0.66)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC

Statistical analysis description:	
Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.	
Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.164 [21]
Method	Wilcoxon (Mann-Whitney)

Notes:

[21] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: Semantic fluency

End point title	Semantic fluency
End point description:	
End point type	Primary
End point timeframe:	
Cognitive performance was measured after each treatment period.	

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	0.02 (± 1.24)	0.09 (± 1.18)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC
Statistical analysis description:	
Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.	
Comparison groups	Subject receiving a high dose of hydrocortisone v Subjects receiving a low dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.536 [22]
Method	Wilcoxon (Mann-Whitney)

Notes:

[22] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: Phonemic fluency

End point title	Phonemic fluency

End point description:

End point type	Primary

End point timeframe:

Cognitive performance was measured after each treatment period.

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	0.32 (± 1.48)	0.21 (± 1.31)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC

Statistical analysis description:

Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.

Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.572 [23]
Method	Wilcoxon (Mann-Whitney)

Notes:

[23] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: Digit span backward

End point title	Digit span backward

End point description:

End point type	Primary

End point timeframe:

Cognitive performance was measured after each treatment period.

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	0.05 (± 0.86)	-0.01 (± 1.02)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC

Statistical analysis description:

Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.

Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.632 [24]
Method	Wilcoxon (Mann-Whitney)

Notes:

[24] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: Trail Making Test - Condition A

End point title	Trail Making Test - Condition A

End point description:

End point type	Primary

End point timeframe:

Cognitive performance was measured after each treatment period.

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	-0.32 (± 1.14)	-0.26 (± 1.06)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC

Statistical analysis description:	
Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.	
Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.512 [25]
Method	Wilcoxon (Mann-Whitney)

Notes:

[25] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: Trail Making Test - Condition B

End point title	Trail Making Test - Condition B
End point description:	
End point type	Primary
End point timeframe:	
Cognitive performance was measured after each treatment period.	

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	0.16 (± 1.46)	0.18 (± 1.31)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC
Statistical analysis description:	
Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.	
Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.861 [26]
Method	Wilcoxon (Mann-Whitney)

Notes:

[26] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: Trail Making Test - Condition B/A

End point title	Trail Making Test - Condition B/A

End point description:

End point type	Primary

End point timeframe:

Cognitive performance was measured after each treatment period.

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	0.37 (± 1.42)	0.36 (± 1.48)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC

Statistical analysis description:

Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.

Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.958 [27]
Method	Wilcoxon (Mann-Whitney)

Notes:

[27] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Primary: Social cognition

End point title	Social cognition

End point description:

End point type	Primary

End point timeframe:

Cognitive performance was measured after each treatment period.

End point values	Subjects receiving a low dose of hydrocortisone	Subject receiving a high dose of hydrocortisone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: Zscore				
arithmetic mean (standard deviation)	-0.67 (± 1.2)	-0.71 (± 1.15)		

Statistical analyses

Statistical analysis title	Low dose of HC versus high dose of HC

Statistical analysis description:

Comparison of cognitive performance on the low dose of hydrocortisone and the high dose of hydrocortisone.

Comparison groups	Subjects receiving a low dose of hydrocortisone v Subject receiving a high dose of hydrocortisone
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.819 [28]
Method	Wilcoxon (Mann-Whitney)

Notes:

[28] - We've applied a Bonferroni correction, setting the significance level at <0.001.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were assessed after 5 and 10 weeks during each treatment period.	
Adverse event reporting additional description:	
Patients were able to report adverse events in between assessment points when necessary.	
Assessment type	Systematic

Dictionary used	
Dictionary name	Not specified
Dictionary version	0

Reporting groups	
Reporting group title	Low dose of hydrocortisone
Reporting group description:	
Adverse events while patients received a low dose of hydrocortisone	
Reporting group title	High dose of hydrocortisone
Reporting group description:	
Adverse events while patients received a high dose of hydrocortisone	

Serious adverse events	Low dose of hydrocortisone	High dose of hydrocortisone	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 58 (1.72%)	1 / 55 (1.82%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events		0	
Vascular disorders			
Minor stroke left cerebral hemisphere	Additional description: A minor stroke in the left cerebral hemisphere		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Influenza A infection	Additional description: Influenza A infection resulting in hospitalization		
subjects affected / exposed	1 / 58 (1.72%)	0 / 55 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Low dose of hydrocortisone	High dose of hydrocortisone	
Total subjects affected by non-serious adverse events subjects affected / exposed	15 / 58 (25.86%)	9 / 55 (16.36%)	
Injury, poisoning and procedural complications			
Broken arm			
subjects affected / exposed	1 / 58 (1.72%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Fall from a horse			
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Motorcycle accident	Additional description: Accident with a motorcycle, knee slightly injured.		
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Cardiac disorders			
Cardiac catherisation			
subjects affected / exposed	1 / 58 (1.72%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Sciatica			
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Tiredness			
subjects affected / exposed	3 / 58 (5.17%)	1 / 55 (1.82%)	
occurrences (all)	3	1	
Dizziness			
subjects affected / exposed	1 / 58 (1.72%)	1 / 55 (1.82%)	
occurrences (all)	1	1	
Headache			
subjects affected / exposed	1 / 58 (1.72%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Stiffness in joints			
subjects affected / exposed	1 / 58 (1.72%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Nausea			

subjects affected / exposed	1 / 58 (1.72%)	1 / 55 (1.82%)	
occurrences (all)	1	1	
Immune system disorders			
Allergic reaction to Ibuprofen			
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Eye disorders			
Diplopia with surgical correction			
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Gasteroenteritis			
subjects affected / exposed	0 / 58 (0.00%)	1 / 55 (1.82%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 58 (3.45%)	0 / 55 (0.00%)	
occurrences (all)	2	0	
Herpes zoster			
subjects affected / exposed	1 / 58 (1.72%)	1 / 55 (1.82%)	
occurrences (all)	1	1	
Red spots in face			
subjects affected / exposed	1 / 58 (1.72%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Acne on back and forehead			
subjects affected / exposed	1 / 58 (1.72%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Depression	Additional description: Progressive depression		
subjects affected / exposed	1 / 58 (1.72%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Cystitis			
subjects affected / exposed	1 / 58 (1.72%)	0 / 55 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			

Joint pain subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	2 / 55 (3.64%) 2	
Infections and infestations Influenza subjects affected / exposed occurrences (all)	2 / 58 (3.45%) 2	1 / 55 (1.82%) 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