Clinical trial results:
Corticosteroids or clobazam for ESES syndrome: a European, multicenter, randomized, controlled clinical trial

Summary

EudraCT number	2013-000531-27
Trial protocol	NL FI ES BE DE GB FR DK IT
Global end of trial date	21 May 2022

Results information

Result version number	v1 (current)
This version publication date	20 April 2024
First version publication date	20 April 2024

Trial information

Trial identification

Sponsor protocol code	NL43510

Additional study identifiers

ISRCTN number	ISRCTN42686094
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Dutch CCMO ABR number: 43510

Notes:

Sponsors

Sponsor organisation name	University Medical Center Utrecht
Sponsor organisation address	Heidelberglaan 100, Utrecht, Netherlands, 3584 CX
Public contact	Marleen van Arnhem - Coordinating investigator, University Medical Center Utrecht, 0031 887555555, m.m.l.vanarnhem-3@umcutrecht.nl
Scientific contact	Floor Jansen - Principal Investigator, University Medical Center Utrecht, 0031 887555555, F.E.Jansen@umcutrecht.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	21 August 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 February 2022
Global end of trial reached?	Yes
Global end of trial date	21 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effects on cognition of treatment with either corticosteroids or clobazam in children with ESES syndrome

Protection of trial subjects:

Yes, by means of proper informed consent forms and a data management plan

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 January 2014
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: 29
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Finland: 5
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 2
Worldwide total number of subjects	45
EEA total number of subjects	44

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)	45
Adolescents (12-17 years)	0

Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study protocol and amendments were reviewed and approved by independent ethics committees or institutional review boards in agreement with local requirements. All parents or legal representatives of children provided written informed consent before enrolment

Pre-assignment

Screening details:

Patients fulfilling the eligibility criteria were consecutively selected by paediatric neurologists during admission or visits at the outpatient clinic at the participating centres. In addition, basic characteristics of patients that were not included in the study despite fulfilment of the eligibility criteria were collected

Period 1

Period 1 title	T0
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Participants were randomly assigned (1:1) to treatment with corticosteroids or clobazam. Participants and treating physicians were not masked to the treatment assignment, because of the inherent differences in mode of administration and expected adverse effects between treatment groups. The neuropsychologists and neurophysiologist (EEG readers) who evaluated the outcome were masked to treatment assignment

Arms

Are arms mutually exclusive?	Yes
Arm title	Corticosteroids

Arm description:

For participants allocated to corticosteroids, either intravenous pulse methylprednisolone or continuous oral prednisolone was given, according to local experience and the preference of each study centre. In the case of pulse methylprednisolone, the dose was 20 mg/kg given over 30 min once daily for 3 consecutive days then at 4-week intervals for 6 months. In the case of oral prednisolone, the dose was initially 2 mg/kg per day, to a maximum of 60 mg per day, for 1 month followed by 1–2 mg/kg per day (maximum 60 mg per day) for the next 5 months (dose decided by the treating physician).

Arm type	Active comparator
Investigational medicinal product name	Methylprednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dose was 20 mg/kg given over 30 min once daily for 3 consecutive days then at 4-week intervals for 6 months

Investigational medicinal product name	Oral prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard + tablet

Routes of administration	Oral use

Dosage and administration details:

The dose was initially 2 mg/kg per day, to a maximum of 60 mg per day, for 1 month followed by 1–2 mg/kg per day (maximum 60 mg per day) for the next 5 months (dose decided by the treating physician).

Arm title	Clobazam

Arm description:

For participants allocated to clobazam, the oral dose was titrated to 0·5 mg/kg per day within 2 weeks. If well tolerated, the dose was increased to a maximum of 1·2 mg/kg, once daily. If the clobazam dose exceeded 20 mg per day, it could be divided in two daily oral administrations. Treatment was continued for at least 6 months. In both treatment groups, if the child developed intolerable adverse effects or further cognitive regression, addition of or replacement with an alternative intervention, including switching to the other treatment group, could be applied as required in the treating physician’s opinion. After 6 months, treatment could either be continued or the dose tapered according to the treating physician’s preference. Alternative treatment options, thereafter, were allowed

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

Dosage and administration details:

The oral dose was titrated to 0·5 mg/kg per day within 2 weeks. If well tolerated, the dose was increased to a maximum of 1·2 mg/kg, once daily. If the clobazam dose exceeded 20 mg per day, it could be divided in two daily oral administrations

Number of subjects in period 1	Corticosteroids	Clobazam
Started	22	23
Completed	22	23

Period 2

Period 2 title	T6
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	Corticosteroids

Arm description:

For participants allocated to corticosteroids, either intravenous pulse methylprednisolone or continuous oral prednisolone was given, according to local experience and the preference of each study centre. In the case of pulse methylprednisolone, the dose was 20 mg/kg given over 30 min once daily for 3 consecutive days then at 4-week intervals for 6 months. In the case of oral prednisolone, the dose was initially 2 mg/kg per day, to a maximum of 60 mg per day, for 1 month followed by 1–2 mg/kg per day (maximum 60 mg per day) for the next 5 months (dose decided by the treating physician).

Arm type	Active comparator
Investigational medicinal product name	Methylprednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dose was 20 mg/kg given over 30 min once daily for 3 consecutive days then at 4-week intervals for 6 months

Investigational medicinal product name	Oral prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard + tablet
Routes of administration	Oral use

Dosage and administration details:

The dose was initially 2 mg/kg per day, to a maximum of 60 mg per day, for 1 month followed by 1–2 mg/kg per day (maximum 60 mg per day) for the next 5 months (dose decided by the treating physician).

Arm title	Clobazam

Arm description:

For participants allocated to clobazam, the oral dose was titrated to 0·5 mg/kg per day within 2 weeks. If well tolerated, the dose was increased to a maximum of 1·2 mg/kg, once daily. If the clobazam dose exceeded 20 mg per day, it could be divided in two daily oral administrations. Treatment was continued for at least 6 months. In both treatment groups, if the child developed intolerable adverse effects or further cognitive regression, addition of or replacement with an alternative intervention, including switching to the other treatment group, could be applied as required in the treating physician’s opinion. After 6 months, treatment could either be continued or the dose tapered according to the treating physician’s preference. Alternative treatment options, thereafter, were allowed

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

Dosage and administration details:

The oral dose was titrated to 0·5 mg/kg per day within 2 weeks. If well tolerated, the dose was increased to a maximum of 1·2 mg/kg, once daily. If the clobazam dose exceeded 20 mg per day, it could be divided in two daily oral administrations

Number of subjects in period 2	Corticosteroids	Clobazam
Started	22	23
Completed	22	21
Not completed	0	2
Consent withdrawn by subject	-	1
Adverse event, non-fatal	-	1

Period 3	
Period 3 title	T18
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Corticosteroids

Arm description:

For participants allocated to corticosteroids, either intravenous pulse methylprednisolone or continuous oral prednisolone was given, according to local experience and the preference of each study centre. In the case of pulse methylprednisolone, the dose was 20 mg/kg given over 30 min once daily for 3 consecutive days then at 4-week intervals for 6 months. In the case of oral prednisolone, the dose was initially 2 mg/kg per day, to a maximum of 60 mg per day, for 1 month followed by 1–2 mg/kg per day (maximum 60 mg per day) for the next 5 months (dose decided by the treating physician).

Arm type	Active comparator
Investigational medicinal product name	Methylprednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dose was 20 mg/kg given over 30 min once daily for 3 consecutive days then at 4-week intervals for 6 months

Investigational medicinal product name	Oral prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard + tablet
Routes of administration	Oral use

Dosage and administration details:

The dose was initially 2 mg/kg per day, to a maximum of 60 mg per day, for 1 month followed by 1–2 mg/kg per day (maximum 60 mg per day) for the next 5 months (dose decided by the treating

physician).

Arm title	Clobazam

Arm description:

For participants allocated to clobazam, the oral dose was titrated to 0·5 mg/kg per day within 2 weeks. If well tolerated, the dose was increased to a maximum of 1·2 mg/kg, once daily. If the clobazam dose exceeded 20 mg per day, it could be divided in two daily oral administrations. Treatment was continued for at least 6 months. In both treatment groups, if the child developed intolerable adverse effects or further cognitive regression, addition of or replacement with an alternative intervention, including switching to the other treatment group, could be applied as required in the treating physician's opinion. After 6 months, treatment could either be continued or the dose tapered according to the treating physician's preference. Alternative treatment options, thereafter, were allowed

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

Dosage and administration details:

The oral dose was titrated to 0·5 mg/kg per day within 2 weeks. If well tolerated, the dose was increased to a maximum of 1·2 mg/kg, once daily. If the clobazam dose exceeded 20 mg per day, it could be divided in two daily oral administrations

Number of subjects in period 3	Corticosteroids	Clobazam
Started	22	21
Completed	21	21
Not completed	1	0
Early termination of trial	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Corticosteroids
Reporting group description:	
For participants allocated to corticosteroids, either intravenous pulse methylprednisolone or continuous oral prednisolone was given, according to local experience and the preference of each study centre. In the case of pulse methylprednisolone, the dose was 20 mg/kg given over 30 min once daily for 3 consecutive days then at 4-week intervals for 6 months. In the case of oral prednisolone, the dose was initially 2 mg/kg per day, to a maximum of 60 mg per day, for 1 month followed by 1–2 mg/kg per day (maximum 60 mg per day) for the next 5 months (dose decided by the treating physician).	
Reporting group title	Clobazam
Reporting group description:	
For participants allocated to clobazam, the oral dose was titrated to 0·5 mg/kg per day within 2 weeks. If well tolerated, the dose was increased to a maximum of 1·2 mg/kg, once daily. If the clobazam dose exceeded 20 mg per day, it could be divided in two daily oral administrations. Treatment was continued for at least 6 months. In both treatment groups, if the child developed intolerable adverse effects or further cognitive regression, addition of or replacement with an alternative intervention, including switching to the other treatment group, could be applied as required in the treating physician's opinion. After 6 months, treatment could either be continued or the dose tapered according to the treating physician's preference. Alternative treatment options, thereafter, were allowed	

Reporting group values	Corticosteroids	Clobazam	Total
Number of subjects	22	23	45
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			
arithmetic mean	7.4	6.1	
standard deviation	± 2.5	± 1.8	-

Gender categorical Units: Subjects			
Female	7	8	15
Male	15	15	30
Complicated perinatal history Units: Subjects			
Yes	13	9	22
No	9	14	23
Febrile seizures Units: Subjects			
Yes	2	5	7
No	20	18	38
Afebrile seizures Units: Subjects			
Yes	15	20	35
No	7	3	10
Seizure type at inclusion Units: Subjects			
Generalised	4	5	9
Focal	11	12	23
No seizures	7	3	10
Generalised and focal	0	3	3
Previously treated with at least one ASM			
Previously treated with at least one antiseizure medications			
Units: Subjects			
Yes	15	18	33
No	7	5	12
Aetiology of EE-SWAS Units: Subjects			
Unknown	10	9	19
Established structural or genetic	12	14	26
MRI abnormalities Units: Subjects			
Yes	10	12	22
No	12	11	23
Metabolic abnormality Units: Subjects			
Yes	0	0	0
No	22	23	45
Genetic abnormality Units: Subjects			
Yes	1	5	6
No	21	18	39
Psychomotor development before EE-SWAS onset Units: Subjects			
Normal (EE-SWAS)	9	9	18
Mildly delayed (developmental EE-SWAS)	8	5	13
Moderately delayed (developmental EE-SWAS)	3	5	8

Severely delayed (developmental EE-SWAS)	2	4	6
Behavioural disorder before EE-SWAS onset Units: Subjects			
Yes	6	4	10
No	16	19	35
EE-SWAS clinical or EEG semiology Units: Subjects			
Typical EE-SWAS	14	18	32
Atypical EE-SWAS	8	5	13
Physiological sleep phenomena present at baseline EEG Units: Subjects			
Yes	13	16	29
No	5	6	11
Unavailable	4	1	5
Age at onset of seizures Units: Years			
arithmetic mean	5.4	3.2	
standard deviation	± 2.8	± 2.3	-
Age at EE-SWAS diagnosis Units: Years			
arithmetic mean	7.2	5.9	
standard deviation	± 2.4	± 1.8	-
Sleep spike-wave index percentage at baseline EEG Units: Percentage			
median	87	90	
inter-quartile range (Q1-Q3)	82 to 93	82 to 95	-
Total IQ at baseline neuropsychological assessment Units: IQ points			
arithmetic mean	76	76	
standard deviation	± 21	± 21	-
Cognitive sum score at baseline Units: Z-score			
arithmetic mean	-1.5	-2.0	
standard deviation	± 1.4	± 1.4	-

End points

End points reporting groups

Reporting group title	Corticosteroids

Reporting group description:

For participants allocated to corticosteroids, either intravenous pulse methylprednisolone or continuous oral prednisolone was given, according to local experience and the preference of each study centre. In the case of pulse methylprednisolone, the dose was 20 mg/kg given over 30 min once daily for 3 consecutive days then at 4-week intervals for 6 months. In the case of oral prednisolone, the dose was initially 2 mg/kg per day, to a maximum of 60 mg per day, for 1 month followed by 1–2 mg/kg per day (maximum 60 mg per day) for the next 5 months (dose decided by the treating physician).

Reporting group title	Clobazam

Reporting group description:

For participants allocated to clobazam, the oral dose was titrated to 0·5 mg/kg per day within 2 weeks. If well tolerated, the dose was increased to a maximum of 1·2 mg/kg, once daily. If the clobazam dose exceeded 20 mg per day, it could be divided in two daily oral administrations. Treatment was continued for at least 6 months. In both treatment groups, if the child developed intolerable adverse effects or further cognitive regression, addition of or replacement with an alternative intervention, including switching to the other treatment group, could be applied as required in the treating physician’s opinion. After 6 months, treatment could either be continued or the dose tapered according to the treating physician’s preference. Alternative treatment options, thereafter, were allowed

Reporting group title	Corticosteroids

Reporting group description:

For participants allocated to corticosteroids, either intravenous pulse methylprednisolone or continuous oral prednisolone was given, according to local experience and the preference of each study centre. In the case of pulse methylprednisolone, the dose was 20 mg/kg given over 30 min once daily for 3 consecutive days then at 4-week intervals for 6 months. In the case of oral prednisolone, the dose was initially 2 mg/kg per day, to a maximum of 60 mg per day, for 1 month followed by 1–2 mg/kg per day (maximum 60 mg per day) for the next 5 months (dose decided by the treating physician).

Reporting group title	Clobazam

Reporting group description:

For participants allocated to clobazam, the oral dose was titrated to 0·5 mg/kg per day within 2 weeks. If well tolerated, the dose was increased to a maximum of 1·2 mg/kg, once daily. If the clobazam dose exceeded 20 mg per day, it could be divided in two daily oral administrations. Treatment was continued for at least 6 months. In both treatment groups, if the child developed intolerable adverse effects or further cognitive regression, addition of or replacement with an alternative intervention, including switching to the other treatment group, could be applied as required in the treating physician’s opinion. After 6 months, treatment could either be continued or the dose tapered according to the treating physician’s preference. Alternative treatment

options, thereafter, were allowed

Reporting group title	Corticosteroids

Reporting group description:

For participants allocated to corticosteroids, either intravenous pulse methylprednisolone or continuous oral prednisolone was given, according to local experience and the preference of each study centre. In the case of pulse methylprednisolone, the dose was 20 mg/kg given over 30 min once daily for 3 consecutive days then at 4-week intervals for 6 months. In the case of oral prednisolone, the dose was initially 2 mg/kg per day, to a maximum of 60 mg per day, for 1 month followed by 1–2 mg/kg per day (maximum 60 mg per day) for the next 5 months (dose decided by the treating physician).

Reporting group title	Clobazam

Reporting group description:

For participants allocated to clobazam, the oral dose was titrated to 0·5 mg/kg per day within 2 weeks. If well tolerated, the dose was increased to a maximum of 1·2 mg/kg, once daily. If the clobazam dose exceeded 20 mg per day, it could be divided in two daily oral administrations. Treatment was continued for at least 6 months. In both treatment groups, if the child developed intolerable adverse effects or further cognitive regression, addition of or replacement with an alternative intervention, including switching to the other treatment group, could be applied as required in the treating physician’s opinion. After 6 months, treatment could either be continued or the dose tapered according to the treating physician’s preference. Alternative treatment options, thereafter, were allowed

Primary: IQ responder T6

End point title	IQ responder T6

End point description:

End point type	Primary

End point timeframe:

T6

End point values	Corticosteroids	Clobazam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	18		
Units: Percentage				
Yes	5	0		
No	15	18		

Statistical analyses

Statistical analysis title	RR ratio
Comparison groups	Corticosteroids v Clobazam
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	10
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	1310.4

Primary: Cognitive sum score responder rate T6	
End point title	Cognitive sum score responder rate T6
End point description:	
End point type	Primary
End point timeframe: T6	

End point values	Corticosteroids	Clobazam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	21		
Units: Percentag				
Yes	1	1		
No	21	20		

Statistical analyses

Statistical analysis title	RR ratio
Comparison groups	Corticosteroids v Clobazam
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.97
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	11.7

Secondary: Delta IQ T6

End point title	Delta IQ T6

End point description:

End point type	Secondary

End point timeframe:
T6

End point values	Corticosteroids	Clobazam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	18		
Units: IQ points				
arithmetic mean (standard deviation)	4.9 (± 9.3)	-0.7 (± 6.2)		

Statistical analyses

Statistical analysis title	Linear regression
Comparison groups	Clobazam v Corticosteroids
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.039
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	10.8

Secondary: Delta cognitive sum score T6

End point title	Delta cognitive sum score T6

End point description:

End point type	Secondary
End point timeframe: T6	

End point values	Corticosteroids	Clobazam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	21		
Units: Z-score				
arithmetic mean (standard deviation)	0.3 (± 0.41)	0.1 (± 0.43)		

Statistical analyses

Statistical analysis title	Linear regression
Comparison groups	Corticosteroids v Clobazam
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.4

Secondary: Delta SWI (%) T6

End point title	Delta SWI (%) T6
End point description:	

End point type	Secondary
End point timeframe: T6	

End point values	Corticosteroids	Clobazam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	21		
Units: Percentage				
median (inter-quartile range (Q1-Q3))	-5 (-55 to 7)	0 (-12 to 4)		

Statistical analyses

Statistical analysis title	Wilcoxon rank-sum test
Comparison groups	Corticosteroids v Clobazam
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.72
Method	Wilcoxon (Mann-Whitney)

Secondary: Global daily functioning (VAS score) T6	
End point title	Global daily functioning (VAS score) T6
End point description:	
End point type	Secondary
End point timeframe: T6	

End point values	Corticosteroids	Clobazam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	16		
Units: VAS score				
arithmetic mean (standard deviation)	1.3 (± 1.3)	1.3 (± 1.0)		

Statistical analyses

Statistical analysis title	Linear regression
Comparison groups	Corticosteroids v Clobazam
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.96
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0.8

Secondary: EEG responder T6

End point title	EEG responder T6
End point description:	

End point type	Secondary
End point timeframe:	
T6	

End point values	Corticosteroids	Clobazam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	21		
Units: Percentage				
Yes	7	4		
No	15	17		

Statistical analyses

Statistical analysis title	RR ratio
Comparison groups	Corticosteroids v Clobazam
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	3.5

Secondary: Sleep SWI <50% T6

End point title	Sleep SWI <50% T6

End point description:

End point type	Secondary

End point timeframe:
T6

End point values	Corticosteroids	Clobazam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	21		
Units: Percentage				
Yes	7	3		
No	15	18		

Statistical analyses

Statistical analysis title	RR ratio
Comparison groups	Clobazam v Corticosteroids
Number of subjects included in analysis	43
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.18
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	1.1

Secondary: Occurrence of seizures T6

End point title	Occurrence of seizures T6

End point description:

End point type	Secondary

End point timeframe:
T6

End point values	Corticosteroids	Clobazam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	21		
Units: Percentage				
Yes	8	9		
No	14	12		

Statistical analyses

Statistical analysis title	RR ratio
Comparison groups	Corticosteroids v Clobazam
Number of subjects included in analysis	43
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.66
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	1.5

Secondary: IQ responder rate T18

End point title	IQ responder rate T18

End point description:

End point type	Secondary

End point timeframe:

T18

End point values	Corticosteroids	Clobazam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	14		
Units: Percentage				
Yes	2	3		
No	15	11		

Statistical analyses

Statistical analysis title	RR ratio
Comparison groups	Corticosteroids v Clobazam
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	2.3

Secondary: Cognitive sum score responder rate T18

End point title	Cognitive sum score responder rate T18
End point description:	
End point type	Secondary
End point timeframe: T18	

End point values	Corticosteroids	Clobazam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Percentage				
Yes	3	2		
No	17	18		

Statistical analyses

Statistical analysis title	RR ratio
Comparison groups	Corticosteroids v Clobazam
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.63
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	1.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	5.9

Secondary: Delta IQ T18

End point title	Delta IQ T18

End point description:

End point type	Secondary

End point timeframe:

T18

End point values	Corticosteroids	Clobazam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	14		
Units: IQ points				
arithmetic mean (standard deviation)	1.2 (± 10.2)	-0.1 (± 12.0)		

Statistical analyses

Statistical analysis title	Linear regression
Comparison groups	Corticosteroids v Clobazam
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.76
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.9
upper limit	9.4

Secondary: Delta cognitive sum scoreT18

End point title	Delta cognitive sum scoreT18

End point description:

End point type	Secondary
End point timeframe: T18	

End point values	Corticosteroids	Clobazam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Z-score				
arithmetic mean (standard deviation)	0.2 (± 0.5)	0.1 (± 0.9)		

Statistical analyses

Statistical analysis title	Linear regression
Comparison groups	Corticosteroids v Clobazam
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.6

Secondary: Delta SWI (%) T18

End point title	Delta SWI (%) T18
End point description:	

End point type	Secondary
End point timeframe: T18	

End point values	Corticosteroids	Clobazam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: Percentage				
median (inter-quartile range (Q1-Q3))	-10 (-39 to 2)	-3 (-55 to 4)		

Statistical analyses

Statistical analysis title	Wilcoxon rank-sum test
Comparison groups	Corticosteroids v Clobazam
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.86
Method	Wilcoxon (Mann-Whitney)

Secondary: Global daily functioning (VAS score) T18

End point title	Global daily functioning (VAS score) T18

End point description:

End point type	Secondary

End point timeframe:

T18

End point values	Corticosteroids	Clobazam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: VAS score				
arithmetic mean (standard deviation)	1.8 (± 1.4)	2.0 (± 1.8)		

Statistical analyses

Statistical analysis title	Linear regression
Comparison groups	Corticosteroids v Clobazam
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.73
Method	Regression, Linear
Parameter estimate	Median difference (final values)
Point estimate	-0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	1.1

Secondary: EEG responder T18

End point title	EEG responder T18
End point description:	

End point type	Secondary
End point timeframe:	
T18	

End point values	Corticosteroids	Clobazam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: Percentage				
Yes	9	6		
No	12	15		

Statistical analyses

Statistical analysis title	RR ratio
Comparison groups	Corticosteroids v Clobazam
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	2.6

Secondary: Sleep SWI <50% T18

End point title	Sleep SWI <50% T18

End point description:

End point type	Secondary

End point timeframe:
T18

End point values	Corticosteroids	Clobazam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: Percentage				
Yes	7	6		
No	14	15		

Statistical analyses

Statistical analysis title	RR ratio
Comparison groups	Corticosteroids v Clobazam
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.74
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.2

Secondary: Occurrence of seizures T18

End point title	Occurrence of seizures T18

End point description:

End point type	Secondary

End point timeframe:
T18

End point values	Corticosteroids	Clobazam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: Percentage				
Yes	8	8		
No	13	13		

Statistical analyses

Statistical analysis title	RR ratio
Comparison groups	Corticosteroids v Clobazam
Number of subjects included in analysis	42
Analysis specification	Post-hoc
Analysis type	superiority
P-value	> 0.99
Method	Regression, Logistic
Parameter estimate	Risk ratio (RR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.8

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Reported at T6

Assessment type	Non-systematic

Dictionary used

Dictionary name	Research Online
Dictionary version	2

Reporting groups

Reporting group title	Corticosteroids

Reporting group description:

For participants allocated to corticosteroids, either intravenous pulse methylprednisolone or continuous oral prednisolone was given, according to local experience and the preference of each study centre. In the case of pulse methylprednisolone, the dose was 20 mg/kg given over 30 min once daily for 3 consecutive days then at 4-week intervals for 6 months. In the case of oral prednisolone, the dose was initially 2 mg/kg per day, to a maximum of 60 mg per day, for 1 month followed by 1–2 mg/kg per day (maximum 60 mg per day) for the next 5 months (dose decided by the treating physician).

Reporting group title	Clobazam

Reporting group description:

For participants allocated to clobazam, the oral dose was titrated to 0·5 mg/kg per day within 2 weeks. If well tolerated, the dose was increased to a maximum of 1·2 mg/kg, once daily. If the clobazam dose exceeded 20 mg per day, it could be divided in two daily oral administrations. Treatment was continued for at least 6 months. In both treatment groups, if the child developed intolerable adverse effects or further cognitive regression, addition of or replacement with an alternative intervention, including switching to the other treatment group, could be applied as required in the treating physician’s opinion. After 6 months, treatment could either be continued or the dose tapered according to the treating physician’s preference. Alternative treatment options, thereafter, were allowed

Serious adverse events	Corticosteroids	Clobazam	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 22 (4.55%)	2 / 21 (9.52%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Seizure aggrevation	Additional description: hospitalisation due to seizure aggravation		

subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory tract infection	Additional description: Hospitalisation due to respiratory tract infection		
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis	Additional description: Hospitalisation due to laryngitis		
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (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: 1 %

Non-serious adverse events	Corticosteroids	Clobazam	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 22 (45.45%)	11 / 21 (52.38%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 22 (9.09%)	2 / 21 (9.52%)	
occurrences (all)	2	2	
Confusion			
subjects affected / exposed	2 / 22 (9.09%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Gait unsteadiness			

subjects affected / exposed	0 / 22 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Fatique			
subjects affected / exposed	2 / 22 (9.09%)	5 / 21 (23.81%)	
occurrences (all)	2	5	
Gastrointestinal disorders			
Loss of appetite			
subjects affected / exposed	1 / 22 (4.55%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
Abdominal pain			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Emotionally unstable			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Depression			
subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Behavioural disturbances			
subjects affected / exposed	2 / 22 (9.09%)	4 / 21 (19.05%)	
occurrences (all)	2	4	
Apathy			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Bed wetting			

subjects affected / exposed	0 / 22 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Endocrine disorders			
Weight gain			
subjects affected / exposed	3 / 22 (13.64%)	2 / 21 (9.52%)	
occurrences (all)	3	2	
Glycosuria			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Intermittent back pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Respiratory infection			
subjects affected / exposed	1 / 22 (4.55%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Otitis media			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Wound infection			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Fever			
subjects affected / exposed	1 / 22 (4.55%)	0 / 21 (0.00%)	
occurrences (all)	1	0	

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

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

We did not reach the targeted sample size, which affects the robustness of the conclusions that can be drawn from the analysis of primary and secondary outcome measures

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33228736