Clinical trial results:
Copenhagen Head Injury Ciclosporin (CHIC) Study:

An open-label, uncontrolled Phase II study to investigate pharmacokinetics, safety and biomarkers of efficacy of NeuroSTAT® (ciclosporin) in patients with severe traumatic brain injury (TBI)

Summary

EudraCT number	2012-000756-34
Trial protocol	DK
Global end of trial date	23 May 2017

Results information

Result version number	v1 (current)
This version publication date	07 June 2018
First version publication date	07 June 2018

Trial information

Trial identification

Sponsor protocol code	2012.001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01825044
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	NeuroVive Pharmaceutical AB
Sponsor organisation address	Medicon Village, Lund, Sweden, SE-223 81
Public contact	Dep. Clinical Trials & Reg. Affairs, NeuroVive Pharmaceutical AB, +46 763393147, matilda.hugerth@neurovive.com
Scientific contact	Dep. Clinical Trials & Reg. Affairs, NeuroVive Pharmaceutical AB, +46 763393147, matilda.hugerth@neurovive.com

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 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 May 2017
Global end of trial reached?	Yes
Global end of trial date	23 May 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To establish safety and to characterise the pharmacokinetic profile of two dosing regimens of ciclosporin in severe Traumatic Brain Injury (TBI) patients.

Protection of trial subjects:

Patients were extensively monitored in the 5 day infusion period. After treatment there was a monitoring period at the intensive care unit of 3 days.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 September 2012
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: 16
Worldwide total number of subjects	16
EEA total number of subjects	16

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)	16
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Date of first enrollment: 03 June 2013
Date of last patient enrollment: 13 June 2016
Single study site in Denmark.

Pre-assignment

Screening details:

Male of female patients aged 18 to 75 years (inclusive) with severe TBI, who required intensive care unit admission and monitoring of intracranial pressure via a ventricular catheter. Clinical examination with post-resuscitation GCS of 4-8, inclusive.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ciclosporin 5 mg/kg/day

Arm description:

2.5 mg/kg ciclosporin intravenous bolus dose infusion (given between 10 to 15 minutes) + continuous intravenous infusion of 5 mg/kg/day ciclosporin for 5 days + 3 days monitoring period, followed by 30 days follow-up period.

Arm type	Experimental
Investigational medicinal product name	NeuroSTAT® (ciclosporin)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Emulsion for infusion
Routes of administration	Intravenous use

Dosage and administration details:

NeuroSTAT® is a sterile intravenous ciclosporin lipid emulsion containing ciclosporin, 5 mg/ml emulsion for infusion. The novel vehicle formulation for ciclosporin is a well-known infusion emulsion, containing e.g. refined soya bean oil and purified structured triglyceride. It is based upon an EU registered and marketed product for parenteral nutrition, manufactured by Fresenius Kabi, Austria (LIPOVENOES® MCT 20%, approved presently in Germany, the Netherlands and Italy).
Dosage: 2.5 mg/kg ciclosporin intravenous bolus dose infusion (given between 10 to 15 minutes) + continuous intravenous infusion of 5 mg/kg/day ciclosporin for 5 days + 3 days monitoring period, followed by 30 days follow-up period.

Arm title	Ciclosporin 10 mg/kg/day

Arm description:

2.5 mg/kg ciclosporin intravenous bolus dose infusion (given between 10 to 15 minutes) + continuous intravenous infusion of 10 mg/kg/day ciclosporin for 5 days (n=10) + 3 days monitoring period, followed by a 30 days follow-up period.

Arm type	Experimental
Investigational medicinal product name	NeuroSTAT® (ciclosporin)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Emulsion for infusion
Routes of administration	Intravenous use

Dosage and administration details:

NeuroSTAT® is a sterile intravenous ciclosporin lipid emulsion containing ciclosporin, 5 mg/ml emulsion

for infusion. The novel vehicle formulation for ciclosporin is a well-known infusion emulsion, containing e.g. refined soya bean oil and purified structured triglyceride. It is based upon an EU registered and marketed product for parenteral nutrition, manufactured by Fresenius Kabi, Austria (LIPOVENOES® MCT 20%, approved presently in Germany, the Netherlands and Italy).
Dosage: 2.5 mg/kg ciclosporin intravenous bolus dose infusion (given between 10 to 15 minutes) + continuous intravenous infusion of 10 mg/kg/day ciclosporin for 5 days + 3 days monitoring period, followed by 30 days follow-up period.

Number of subjects in period 1	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day
Started	10	6
Completed	10	6

Period 2

Period 2 title	Treatment and Follow up
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ciclosporin 5 mg/kg/day

Arm description:

2.5 mg/kg ciclosporin intravenous bolus dose infusion (given between 10 to 15 minutes) + continuous intravenous infusion of 5 mg/kg/day ciclosporin for 5 days + 3 days monitoring period, followed by 30 days follow-up period.

Arm type	Experimental
Investigational medicinal product name	NeuroSTAT®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Emulsion for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

NeuroSTAT® is a sterile intravenous ciclosporin lipid emulsion containing ciclosporin, 5 mg/ml emulsion for infusion. The novel vehicle formulation for ciclosporin is a well-known infusion emulsion, containing e.g. refined soya bean oil and purified structured triglyceride. It is based upon an EU registered and marketed product for parenteral nutrition, manufactured by Fresenius Kabi, Austria (LIPOVENOES® MCT 20%, approved presently in Germany, the Netherlands and Italy).
Dosage: 2.5 mg/kg ciclosporin intravenous bolus dose infusion (given between 10 to 15 minutes) + continuous intravenous infusion of 5 mg/kg/day ciclosporin for 5 days + 3 days monitoring period, followed by 30 days follow-up period.

Arm title	Ciclosporin 10 mg/kg/day

Arm description:

2.5 mg/kg ciclosporin intravenous bolus dose infusion (given between 10 to 15 minutes) + continuous intravenous infusion of 10 mg/kg/day ciclosporin for 5 days (n=10) + 3 days monitoring period, followed by a 30 days follow-up period.

Arm type	Experimental
Investigational medicinal product name	NeuroSTAT®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Emulsion for infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

NeuroSTAT® is a sterile intravenous ciclosporin lipid emulsion containing ciclosporin, 5 mg/ml emulsion for infusion. The novel vehicle formulation for ciclosporin is a well-known infusion emulsion, containing e.g. refined soya bean oil and purified structured triglyceride. It is based upon an EU registered and marketed product for parenteral nutrition, manufactured by Fresenius Kabi, Austria (LIPOVENOES® MCT 20%, approved presently in Germany, the Netherlands and Italy).
Dosage: 2.5 mg/kg ciclosporin intravenous bolus dose infusion (given between 10 to 15 minutes) + continuous intravenous infusion of 10 mg/kg/day ciclosporin for 5 days + 3 days monitoring period, followed by 30 days follow-up period.

Number of subjects in period 2	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day
Started	10	6
Completed	10	6

Baseline characteristics

Reporting groups	
Reporting group title	Ciclosporin 5 mg/kg/day
Reporting group description:	
2.5 mg/kg ciclosporin intravenous bolus dose infusion (given between 10 to 15 minutes) + continuous intravenous infusion of 5 mg/kg/day ciclosporin for 5 days + 3 days monitoring period, followed by 30 days follow-up period.	
Reporting group title	Ciclosporin 10 mg/kg/day
Reporting group description:	
2.5 mg/kg ciclosporin intravenous bolus dose infusion (given between 10 to 15 minutes) + continuous intravenous infusion of 10 mg/kg/day ciclosporin for 5 days (n=10) + 3 days monitoring period, followed by a 30 days follow-up period.	

Reporting group values	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day	Total
Number of subjects	10	6	16
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	10	6	16
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	34.50	37.33	
standard deviation	± 14.42	± 14.38	-
Gender categorical Units: Subjects			
Female	3	1	4
Male	7	5	12

End points

End points reporting groups

Reporting group title	Ciclosporin 5 mg/kg/day
Reporting group description:	
2.5 mg/kg ciclosporin intravenous bolus dose infusion (given between 10 to 15 minutes) + continuous intravenous infusion of 5 mg/kg/day ciclosporin for 5 days + 3 days monitoring period, followed by 30 days follow-up period.	
Reporting group title	Ciclosporin 10 mg/kg/day
Reporting group description:	
2.5 mg/kg ciclosporin intravenous bolus dose infusion (given between 10 to 15 minutes) + continuous intravenous infusion of 10 mg/kg/day ciclosporin for 5 days (n=10) + 3 days monitoring period, followed by a 30 days follow-up period.	
Reporting group title	Ciclosporin 5 mg/kg/day
Reporting group description:	
2.5 mg/kg ciclosporin intravenous bolus dose infusion (given between 10 to 15 minutes) + continuous intravenous infusion of 5 mg/kg/day ciclosporin for 5 days + 3 days monitoring period, followed by 30 days follow-up period.	
Reporting group title	Ciclosporin 10 mg/kg/day
Reporting group description:	
2.5 mg/kg ciclosporin intravenous bolus dose infusion (given between 10 to 15 minutes) + continuous intravenous infusion of 10 mg/kg/day ciclosporin for 5 days (n=10) + 3 days monitoring period, followed by a 30 days follow-up period.	

Primary: Adverse Events

End point title	Adverse Events[1]
End point description:	
Total number of adverse events during treatment and after end of study drug administration (follow-up).	
End point type	Primary
End point timeframe:	
During treatment and after end of study drug administration (follow-up).	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical analysis for this endpoint. Only summary statistics are presented.

End point values	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Adverse Events				
Total No. of AEs	69	47		
Total No. of unique AEs	65	47		
Total No. of patients with at least 1 AE	10	6		
Total No. of unique related AEs	8	13		
Total No. of related AEs	8	13		
Total No. patients with at least 1 related AE	4	5		
Total No. of SAEs	0	1		
Total No. of patients with at least 1 SAE	0	1		

Total No. of patients with AE leading to discont.	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with positive infectious symptom abnormalities

End point title	Number of subjects with positive infectious symptom abnormalities[2]

End point description:

Assessment of infections: abnormality assessed as Yes/No according to standard procedures at intensive care unit.

End point type	Primary

End point timeframe:

From screening until Day 8.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical analysis for this endpoint. Only summary statistics are presented.

End point values	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Number of Subjects				
Screening/Enrolment	0	1		
Treatment, Day 2	0	0		
Treatment, Day 3	0	1		
Treatment, Day 4	1	2		
Treatment, Day 5	0	1		
Monitoring, Day 1	0	3		
Monitoring, Day 2	2	1		
Monitoring, Day 3	1	0		

Statistical analyses

No statistical analyses for this end point

Primary: Intracranial pressure

End point title	Intracranial pressure[3]

End point description:

For intracranial pressure (ICP), several measurements were made each day.
Post-baseline values within each patient were averaged within day before summary statistics were derived.

End point type	Primary

End point timeframe:

From baseline (last observation before bolus dose).

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical analysis for this endpoint. Only summary statistics are presented.

End point values	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Observed values (mmHg)				
median (full range (min-max))				
Baseline	8.0 (-1 to 22)	16.0 (13 to 18)		
Treatment Day 1	12.3 (2 to 18)	14.8 (7 to 16)		
Treatment Day 2	13.9 (2 to 19)	13.5 (8 to 15)		
Treatment Day 3	12.8 (1 to 23)	12.1 (8 to 16)		
Treatment Day 4	12.0 (4 to 19)	15.0 (8 to 19)		
Treatment Day 5	13.6 (10 to 19)	11.6 (7 to 21)		
Monitoring Day 1	14.6 (10 to 18)	12.0 (1 to 17)		
Monitoring Day 2	12.8 (3 to 21)	12.8 (2 to 15)		
Monitoring Day 3	12.7 (3 to 23)	13.9 (12 to 15)		

Statistical analyses

No statistical analyses for this end point

Primary: Markers of hepatic function-Alanine Aminotransferase

End point title	Markers of hepatic function-Alanine Aminotransferase[4]

End point description:

Blood samples were taken at protocol specified time points and alanine aminotransferase was assessed as a marker of hepatic function.

End point type	Primary

End point timeframe:

Measurements made at, baseline, during the five days of treatment and until Day 3 following completion of treatment.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical analysis for this endpoint. Only summary statistics are presented.

End point values	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Observed Values (U/L)				
median (full range (min-max))				
Baseline	89.0 (14 to 252)	32.0 (18 to 83)		
Treatment Day 1	41.0 (16 to 215)	28.0 (17 to 47)		

Treatment Day 2	36.0 (15 to 261)	26.0 (15 to 43)		
Treatment Day 3	46.5 (17 to 224)	41.0 (15 to 63)		
Treatment Day 4	48.5 (22 to 171)	43 (21 to 81)		
Treatment Day 5	67.0 (24 to 165)	35.0 (21 to 78)		
Monitoring Day 1	65.1 (26 to 145)	34.0 (16 to 78)		
Monitoring Day 2	64.0 (30 to 183)	58.0 (26 to 110)		
Monitoring Day 3	69.0 (28 to 159)	66.5 (23 to 128)		

Statistical analyses

No statistical analyses for this end point

Primary: Markers of hepatic function-Aspartate Aminotransferase

End point title	Markers of hepatic function-Aspartate Aminotransferase[5]

End point description:

Blood samples were taken at protocol specified time points and Aspartate Aminotransferase was assessed as a marker of hepatic function.

End point type	Primary

End point timeframe:

Measurements made at, baseline, during the five days of treatment and until Day 3 following completion of treatment.

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical analysis for this endpoint. Only summary statistics are presented.

End point values	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Observed values (U/L)				
median (full range (min-max))				
Baseline	143 (27 to 264)	50.0 (22 to 89)		
Treatment Day 1	42 (24 to 190)	37.0 (32 to 75)		
Treatment Day 2	31.5 (24 to 245)	43.0 (30 to 76)		
Treatment Day 3	35.5 (17 to 184)	64.5 (42 to 109)		
Treatment Day 4	51.5 (25 to 151)	46.0 (28 to 99)		
Treatment Day 5	73 (37 to 123)	58.0 (20 to 128)		
Monitoring Day 1	55.5 (32 to 134)	50.0 (16 to 79)		
Monitoring Day 2	66.5 (35 to 162)	64.0 (33 to 124)		

Monitoring Day 3	54.5 (26 to 163)	56.0 (29 to 147)		

Statistical analyses

No statistical analyses for this end point

Primary: Markers of hepatic function-Bilirubin

End point title	Markers of hepatic function-Bilirubin[6]

End point description:

Blood samples were taken at protocol specified time points and bilirubin was assessed as a marker of hepatic function.

End point type	Primary

End point timeframe:

Measurements made at, baseline, during the five days of treatment and until Day 3 following completion of treatment.

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical analysis for this endpoint. Only summary statistics are presented.

End point values	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Observed values (umol/L)				
median (full range (min-max))				
Baseline	8.0 (3 to 14)	4.5 (3 to 22)		
Treatment Day 1	11.0 (5 to 34)	11.5 (7 to 24)		
Treatment Day 2	14.5 (4 to 31)	17.5 (8 to 36)		
Treatment Day 3	16 (4 to 48)	23.5 (9 to 101)		
Treatment Day 4	20.0 (3 to 42)	51.0 (8 to 106)		
Treatment Day 5	15.0 (4 to 42)	47.0 (6 to 117)		
Monitoring Day 1	13.5 (3 to 35)	55.0 (4 to 70)		
Monitoring Day 2	10.0 (3 to 23)	24.5 (3 to 36)		
Monitoring Day 3	8.0 (4 to 19)	16.5 (4 to 28)		

Statistical analyses

No statistical analyses for this end point

Primary: Markers of hepatic function- Prothrombin INR

End point title	Markers of hepatic function- Prothrombin INR[7]

End point description:

Blood samples were taken at protocol specified time points and assessed for Prothrombin INR as a marker of hepatic function.

End point type	Primary

End point timeframe:

Measurements made at, baseline, during the five days of treatment and until Day 3 following completion of treatment.

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical analysis for this endpoint. Only summary statistics are presented.

End point values	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Observed values				
median (full range (min-max))				
Baseline	1.15 (1.0 to 1.5)	1.15 (1.0 to 1.5)		
Treatment Day 1	1.30 (1.1 to 1.5)	1.15 (1.1 to 1.4)		
Treatment Day 2	1.20 (1.1 to 1.3)	1.15 (1.0 to 1.6)		
Treatment Day 3	1.20 (1.1 to 1.3)	1.25 (1.0 to 1.5)		
Treatment Day 4	1.20 (1.1 to 1.4)	1.20 (0.9 to 1.4)		
Treatment Day 5	1.10 (1.0 to 1.2)	1.20 (0.9 to 1.3)		
Monitoring Day 1	1.10 (1.0 to 1.1)	1.10 (0.9 to 1.3)		
Monitoring Day 2	1.00 (1.0 to 1.2)	1.10 (1.0 to 1.2)		
Monitoring Day 3	1.00 (0.9 to 1.1)	1.00 (1.0 to 1.0)		

Statistical analyses

No statistical analyses for this end point

Primary: Markers of renal function - Creatinine

End point title	Markers of renal function - Creatinine[8]

End point description:

Blood samples were taken at protocol specified time points and assessed for creatinine as a marker of renal function.

End point type	Primary

End point timeframe:

Measurements made at, baseline, during the five days of treatment and until Day 3 following completion of treatment.

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical analysis for this endpoint. Only summary statistics are presented.

End point values	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Observed values (umol/L)				
median (full range (min-max))				
Baseline	62.0 (52 to 84)	69.0 (38 to 108)		
Treatment Day 1	68.0 (49 to 119)	72.0 (54 to 100)		
Treatment Day 2	69.5 (53 to 163)	80.0 (61 to 104)		
Treatment Day 3	70.5 (56 to 215)	80.5 (52 to 192)		
Treatment Day 4	70.5 (54 to 277)	104.5 (51 to 296)		
Treatment Day 5	67.5 (53 to 258)	92.0 (47 to 267)		
Monitoring Day 1	65.0 (50 to 250)	105.0 (39 to 424)		
Monitoring Day 2	54.5 (45 to 186)	90.0 (40 to 327)		
Monitoring Day 3	53.5 (37 to 108)	65.5 (38 to 350)		

Statistical analyses

No statistical analyses for this end point

Primary: Markers of renal function - Cystatin C

End point title	Markers of renal function - Cystatin C[9]

End point description:

Blood samples were taken at protocol specified time points and assessed for cystatin C as a marker of renal function.

End point type	Primary

End point timeframe:

Measurements made at, baseline, during the five days of treatment and until Day 3 following completion of treatment.

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical analysis for this endpoint. Only summary statistics are presented.

End point values	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Observed values (mg/L)				
median (full range (min-max))				
Baseline	0.66 (0.5 to 1.1)	0.88 (0.8 to 1.4)		
Treatment Day 1	0.90 (0.6 to 1.2)	0.83 (0.6 to 1.5)		
Treatment Day 2	0.86 (0.6 to 1.6)	0.93 (0.8 to 1.2)		

Treatment Day 3	0.86 (0.6 to 1.6)	1.20 (1.0 to 1.7)		
Treatment Day 4	0.96 (0.7 to 2.0)	1.40 (1.1 to 2.6)		
Treatment Day 5	1.00 (0.7 to 1.9)	1.50 (1.0 to 2.9)		
Monitoring Day 1	1.00 (0.7 to 2.1)	1.40 (1.0 to 1.8)		
Monitoring Day 2	1.00 (0.8 to 1.7)	1.40 (1.4 to 1.4)		
Monitoring Day 3	0.8 (0.7 to 1.7)	1.10 (1.0 to 1.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Markers of renal function - Urea Nitrogen

End point title	Markers of renal function - Urea Nitrogen[10]

End point description:

Blood samples were taken at protocol specified time points and assessed for urea nitrogen as a marker of renal function.

End point type	Primary

End point timeframe:

Measurements made at, baseline, during the five days of treatment and until Day 3 following completion of treatment.

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical analysis for this endpoint. Only summary statistics are presented.

End point values	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Observed values (mmol/L)				
median (full range (min-max))				
Baseline	2.70 (2.1 to 4.6)	4.10 (2.0 to 10.9)		
Treatment Day 1	3.10 (1.5 to 5.2)	3.80 (2.5 to 7.4)		
Treatment Day 2	4.05 (2.5 to 7.4)	5.10 (2.8 to 9.5)		
Treatment Day 3	5.40 (3.3 to 9.0)	8.00 (5.4 to 9.9)		
Treatment Day 4	6.95 (3.8 to 13.1)	11.00 (6.9 to 12.3)		
Treatment Day 5	8.65 (5.3 to 18.1)	11.90 (7.2 to 15.9)		
Monitoring Day 1	9.40 (6.6 to 21.4)	15.95 (7.4 to 24.6)		
Monitoring Day 2	7.40 (4.6 to 16.7)	13.60 (7.2 to 22.6)		
Monitoring Day 3	5.95 (4.3 to 9.4)	10.20 (6.6 to 27.2)		

Statistical analyses

No statistical analyses for this end point

Primary: Clearance

End point title	Clearance[11]

End point description:

PK paramters were based on ciclosporin levels in blood.
Clearance (CL), primary pharmacokinetic parameter of population pharmacokinetic analysis

End point type	Primary

End point timeframe:

From start of bolus infusion to end of monitoring period (Day 8).

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical analysis for this endpoint. Only summary statistics are presented.

End point values	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: L/h				
arithmetic mean (standard deviation)	24.3 (± 5.82)	24.6 (± 4.52)		

Statistical analyses

No statistical analyses for this end point

Primary: Volume of distribution of the central compartment

End point title	Volume of distribution of the central compartment[12]

End point description:

PK parameters based on ciclosporin levels in blood.
Volume of distribution of the central compartment (Vc), primary pharmacokinetic parameter of population pharmacokinetic analysis.

End point type	Primary

End point timeframe:

From start of bolus infusion to end of monitoring period (Day 8).

Notes:

[12] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical analysis for this endpoint. Only summary statistics are presented.

End point values	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Litres				
arithmetic mean (standard deviation)	29.1 (± 46.3)	21.5 (± 7.19)		

Statistical analyses

No statistical analyses for this end point

Primary: The volume of distribution of the peripheral compartments

End point title	The volume of distribution of the peripheral compartments[13]

End point description:

PK parameters based on ciclosporin levels in blood.
Volume of distribution of the peripheral compartment (Vp), primary pharmacokinetic parameter of population pharmacokinetic analysis.
Vp1 is the first peripheral volume of distribution, Vp2 is the second peripheral volume of distribution

End point type	Primary

End point timeframe:

From start of bolus infusion to end of monitoring period (Day 8).

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical analysis for this endpoint. Only summary statistics are presented.

End point values	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Litres				
arithmetic mean (standard deviation)				
Vp1	46.9 (± 7.65)	50.5 (± 5.68)		
Vp2	373 (± 81.1)	398 (± 66.2)		

Statistical analyses

No statistical analyses for this end point

Primary: Mean concentration at steady state

End point title	Mean concentration at steady state[14]

End point description:

PK parameters based on ciclosporin levels in blood.
Mean concentration at steady state
Cav,ss = Dose rate/CL

End point type	Primary

End point timeframe:

From start of bolus infusion to end of monitoring period (Day 8).

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical analysis for this endpoint. Only summary statistics are presented.

End point values	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: ng/mL				
arithmetic mean (standard deviation)	665 (± 117)	1320 (± 279)		

Statistical analyses

No statistical analyses for this end point

Primary: The observed maximum plasma concentration after single dose administration

End point title	The observed maximum plasma concentration after single dose administration[15]

End point description:

PK parameters based on ciclosporin levels in blood:
The observed maximum plasma concentration (Cmax) after single dose administration.

End point type	Primary

End point timeframe:

From start of bolus infusion to end of monitoring period (Day 8).

Notes:

[15] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical analysis for this endpoint. Only summary statistics are presented.

End point values	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: ng/mL				
arithmetic mean (standard deviation)	4420 (± 2350)	4930 (± 511)		

Statistical analyses

No statistical analyses for this end point

Primary: The time to reach Cmax

End point title	The time to reach Cmax[16]

End point description:

PK parameters based on ciclosporin levels in blood:
Tmax, the time to reach Cmax.

End point type	Primary

End point timeframe:

From start of bolus infusion to end of monitoring period (Day 8).

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical analysis for this endpoint. Only summary statistics are presented.

End point values	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Hours				
median (full range (min-max))	0.250 (0.250 to 0.417)	0.308 (0.250 to 0.417)		

Statistical analyses

No statistical analyses for this end point

Primary: The area under the concentration vs. time curve

End point title	The area under the concentration vs. time curve[17]

End point description:

PK parameters based on ciclosporin levels in blood:
Total area under the concentration curve vs. time curve (AUC) to infinity.

End point type	Primary

End point timeframe:

From start of bolus infusion to end of monitoring period (Day 8).

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical analysis for this endpoint. Only summary statistics are presented.

End point values	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: mg.h/L				
arithmetic mean (standard deviation)	87.5 (± 15.3)	155 (± 30.2)		

Statistical analyses

No statistical analyses for this end point

Primary: AUC to the last quantifiable concentration

End point title	AUC to the last quantifiable concentration[18]

End point description:

PK parameters based on ciclosporin levels in blood:
AUC0-t, the area under the concentration vs. time curve from time zero to the last quantifiable concentration (Clast, obs).

End point type	Primary

End point timeframe:

From start of bolus infusion to end of monitoring period (Day 8).

Notes:

[18] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical analysis for this endpoint. Only summary statistics are presented.

End point values	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: mg.h/L				
arithmetic mean (standard deviation)	82.5 (± 12.6)	146 (± 29.2)		

Statistical analyses

No statistical analyses for this end point

Primary: Extrapolated area under the curve from t last to infinity

End point title	Extrapolated area under the curve from t last to infinity[19]

End point description:

PK parameters based on ciclosporin levels in blood:
AUCextr, extrapolated area under the curve from t last to infinity.

End point type	Primary

End point timeframe:

From start of bolus infusion to end of monitoring period (Day 8).

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical analysis for this endpoint. Only summary statistics are presented.

End point values	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Percent (%)				
arithmetic mean (standard deviation)	5.10 (± 2.75)	5.88 (± 2.60)		

Statistical analyses

No statistical analyses for this end point

Primary: The apparent elimination half-life

End point title	The apparent elimination half-life[20]

End point description:

PK parameters based on ciclosporin levels in blood:
t½ the apparent elimination half-life, calculated based on CL, Vc, Q, and Vp

End point type	Primary

End point timeframe:

From start of bolus infusion to end of monitoring period (Day 8).

Notes:

[20] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There was no statistical analysis for this endpoint. Only summary statistics are presented.

End point values	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	6		
Units: Hours				
arithmetic mean (standard deviation)	43.5 (± 11.3)	46.0 (± 8.06)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from the time of infusion start through end of Day 8.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Ciclosporin 5 mg/kg/day

Reporting group description:

2.5 mg/kg ciclosporin intravenous bolus dose infusion (given between 10 to 15 minutes) + continuous intravenous infusion of 5 mg/kg/day ciclosporin for 5 days + 3 days monitoring period, followed by 30 days follow-up period.

Reporting group title	Ciclosporin 10 mg/kg/day

Reporting group description:

2.5 mg/kg ciclosporin intravenous bolus dose infusion (given between 10 to 15 minutes) + continuous intravenous infusion of 10 mg/kg/day ciclosporin for 5 days (n=10) + 3 days monitoring period, followed by a 30 days follow-up period.

Serious adverse events	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Renal and urinary disorders			
Renal tubular necrosis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Ciclosporin 5 mg/kg/day	Ciclosporin 10 mg/kg/day	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	6 / 6 (100.00%)	
Investigations			
Amylase increased			

subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Blood albumin decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Blood creatinine abnormal			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
subjects affected / exposed	1 / 10 (10.00%)	2 / 6 (33.33%)	
occurrences (all)	1	2	
Blood magnesium decreased			
subjects affected / exposed	2 / 10 (20.00%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
Blood phosphorus decreased			
subjects affected / exposed	4 / 10 (40.00%)	3 / 6 (50.00%)	
occurrences (all)	4	3	
Blood potassium increased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Blood urea increased			
subjects affected / exposed	2 / 10 (20.00%)	2 / 6 (33.33%)	
occurrences (all)	2	2	
Blood zinc decreased			
subjects affected / exposed	3 / 10 (30.00%)	3 / 6 (50.00%)	
occurrences (all)	3	3	
Body temperature increased			
subjects affected / exposed	2 / 10 (20.00%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
C-reactive protein increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Cystatin C increased			
subjects affected / exposed	3 / 10 (30.00%)	2 / 6 (33.33%)	
occurrences (all)	3	2	
Hepatic enzyme increased			

subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
International normalised ratio increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Myoglobin blood increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Pupillary light reflex tests abnormal			
subjects affected / exposed	3 / 10 (30.00%)	1 / 6 (16.67%)	
occurrences (all)	4	1	
Platelet count increased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Blood bilirubin increased			
subjects affected / exposed	0 / 10 (0.00%)	4 / 6 (66.67%)	
occurrences (all)	0	4	
Blood calcium decreased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Intracranial pressure increased			

subjects affected / exposed	3 / 10 (30.00%)	1 / 6 (16.67%)	
occurrences (all)	4	1	
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	2 / 10 (20.00%)	1 / 6 (16.67%)	
occurrences (all)	3	1	
Face oedema			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	8 / 10 (80.00%)	5 / 6 (83.33%)	
occurrences (all)	9	5	
Impaired gastric emptying			
subjects affected / exposed	6 / 10 (60.00%)	2 / 6 (33.33%)	
occurrences (all)	6	2	
Subileus			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Oliguria			
subjects affected / exposed	0 / 10 (0.00%)	5 / 6 (83.33%)	
occurrences (all)	0	5	
Renal tubular necrosis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			

Bacteraemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Candida infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Oral herpes			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	3 / 10 (30.00%)	3 / 6 (50.00%)	
occurrences (all)	3	3	
Urinary tract infection			
subjects affected / exposed	2 / 10 (20.00%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Sepsis			
subjects affected / exposed	0 / 10 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	3 / 10 (30.00%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
Hypervolaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Hyperkalaemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 November 2013	Change in inclusion criterion no 4: requirement to conduct a wake-up call to assess GCS score was removed.
28 August 2014	Change in inclusion criterion no 5 and change in study assessments.
24 September 2015	Change in inclusion criterion no 1, upper age limited increased from 65 to 75 years. Addition of exclusion criterion no 15.
25 January 2016	Microdialysis measurements of metabolic biomarkers and brain tissue oxygen measurements were made optional.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

It had been planned to include ten patients in the higher dose group but the study was prematurely closed due to slow recruitment.

Notes: