Clinical trial results:
A Phase I/II study to evaluate the safety and pharmacokinetics of intravenous Trappsol® Cyclo™ (HP-Beta-CD) in patients with Niemann-Pick disease type C (NPC-1) and the pharmacodynamic effects of treatment upon markers of cholesterol metabolism and clinical outcomes

Summary

EudraCT number	2015-005761-23
Trial protocol	GB SE IT
Global end of trial date	03 March 2021

Results information

Result version number	v1 (current)
This version publication date	23 July 2022
First version publication date	23 July 2022

Trial information

Trial identification

Sponsor protocol code	CTD-TCNPC-201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02912793
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cyclo Therapeutics, Inc.
Sponsor organisation address	6714 NW 16th Street, Suite B, Gainesville, United States, FL 32653
Public contact	Lise Kjems, MD PhD, CMO, Cyclo Therapeutics, Inc., lise.kjems@cyclodex.com
Scientific contact	Lise Kjems, MD PhD, CMO, Cyclo Therapeutics, Inc., lise.kjems@cyclodex.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	03 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 March 2021
Global end of trial reached?	Yes
Global end of trial date	03 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Stage 1
• To compare the plasma pharmacokinetics of hydroxypropyl-β-cyclodextrin following three different single doses of intravenous Trappsol® in patients with NPC-1

Stage 2
• To evaluate the efficacy and tolerability of three different doses of Trappsol® in the management of clinical manifestations of NPC-1

Protection of trial subjects:

This study was conducted in full conformance with the International Conference on Harmonisation (ICH) E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki (October 2013), or the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. Safety of the subjects was safeguarded through safety data review throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 September 2016
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	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Israel: 6
Worldwide total number of subjects	12
EEA total number of subjects	1

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)	8
Adolescents (12-17 years)	1
Adults (18-64 years)	3
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First patient in on 20th Jun 2017 and last patient out on 3rd Mar 2021. All patients recruited to hospital clinics.

Pre-assignment

Screening details:

13 patients were screened for up to 28 days before entry. One patient was excluded due to screen failure.

Pre-assignment period milestones

Number of subjects started	13[1]
Number of subjects completed	12

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Failed screening: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 13 patients were screened for up to 28 days before entry. One patient was excluded due to screen failure.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Blinding implementation details:

Study drug was prepared by an on-site pharmacist; therefore, the blind for the Principal Investigator, site personnel and patient could be maintained. PK bioanalytical personnel and drug accountability monitors were unblinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Trappsol® Cyclo™ IV 1500 mg/kg

Arm description:

HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks.

Arm type	Active comparator
Investigational medicinal product name	Trappsol® Cyclo™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks at a dose of 1500 mg/kg.

Arm title	Trappsol® Cyclo™ IV 2000 mg/kg

Arm description:

HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks.

Arm type	Active comparator
Investigational medicinal product name	Trappsol® Cyclo™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks at a dose of 2000 mg/kg.

Arm title	Trappsol® Cyclo™ IV 2500 mg/kg

Arm description:

HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks

Arm type	Active comparator
Investigational medicinal product name	Trappsol® Cyclo™
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks at a dose of 2500 mg/kg.

Number of subjects in period 1	Trappsol® Cyclo™ IV 1500 mg/kg	Trappsol® Cyclo™ IV 2000 mg/kg	Trappsol® Cyclo™ IV 2500 mg/kg
Started	5	4	3
Completed	2	4	3
Not completed	3	0	0
Physician decision	1	-	-
Consent withdrawn by subject	1	-	-
Unable to travel due to Covid restrictions	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Trappsol® Cyclo™ IV 1500 mg/kg
Reporting group description:	
HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks.	
Reporting group title	Trappsol® Cyclo™ IV 2000 mg/kg
Reporting group description:	
HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks.	
Reporting group title	Trappsol® Cyclo™ IV 2500 mg/kg
Reporting group description:	
HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks	

Reporting group values	Trappsol® Cyclo™ IV 1500 mg/kg	Trappsol® Cyclo™ IV 2000 mg/kg	Trappsol® Cyclo™ IV 2500 mg/kg
Number of subjects	5	4	3
Age categorical Units: Subjects			
Children (2-11 years)	3	3	2
Adolescents (12-17 years)	1	0	0
Adults (18-64 years)	1	1	1
Age continuous Units: years			
arithmetic mean	12.2	13.5	10.7
full range (min-max)	2 to 34	2 to 39	3 to 21
Gender categorical Units: Subjects			
Female	3	1	1
Male	2	3	2
Race Units: Subjects			
White	4	4	3
Black/African	1	0	0
Weight Units: Kg			
arithmetic mean	25	34.5	30.0
full range (min-max)	11 to 58	13 to 68	15 to 45
17-Domain Niemann-Pick disease Type C-Clinical Severity Scale Units: Points on scale 0-61			
arithmetic mean	21.0	15.5	17.7
standard deviation	± 9.25	± 7.42	± 5.69

Reporting group values	Total		
Number of subjects	12		

Age categorical Units: Subjects			
Children (2-11 years)	8		
Adolescents (12-17 years)	1		
Adults (18-64 years)	3		
Age continuous Units: years arithmetic mean full range (min-max)	- -		
Gender categorical Units: Subjects			
Female	5		
Male	7		
Race Units: Subjects			
White	11		
Black/African	1		
Weight Units: Kg arithmetic mean full range (min-max)	- -		
17-Domain Niemann-Pick disease Type C-Clinical Severity Scale Units: Points on scale 0-61 arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Trappsol® Cyclo™ IV 1500 mg/kg
Reporting group description:	
HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks.	
Reporting group title	Trappsol® Cyclo™ IV 2000 mg/kg
Reporting group description:	
HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks.	
Reporting group title	Trappsol® Cyclo™ IV 2500 mg/kg
Reporting group description:	
HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks	
Subject analysis set title	Across the dose range
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients who were assigned to a treatment regimen (randomized, even if not dosed) constituted the ITT population. The ITT population was analyzed using the treatment assigned in the randomization schedule even if a patient was dosed incorrectly.	

Primary: To Evaluate the Plasma Pharmacokinetics of 3 Doses of Trappsol® by Measurement of Plasma Levels (Cmax)

End point title	To Evaluate the Plasma Pharmacokinetics of 3 Doses of Trappsol® by Measurement of Plasma Levels (Cmax)[1]
End point description:	
To evaluate plasma PK of Trappsol® by comparison of Maximum Concentration (Cmax) of the three doses.	
End point type	Primary
End point timeframe:	
0,2,4,6,& 8 hours (h) after the start of the IV infusion of Trappsol® and 0.5,1,2,4,8 & 12 h after the end of the infusion	

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: Quantitative statistical analysis was not performed for this PK endpoint. Descriptive statistics are included.

End point values	Trappsol® Cyclo™ IV 1500 mg/kg	Trappsol® Cyclo™ IV 2000 mg/kg	Trappsol® Cyclo™ IV 2500 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	3[2]	3	
Units: ng/ml				
arithmetic mean (standard deviation)	1272600 (± 489692)	1856667 (± 803140)	1920000 (± 121655)	

Notes:

[2] - Sample missing for 1 patient

Statistical analyses

No statistical analyses for this end point

Primary: To Evaluate the Plasma Pharmacokinetics of 3 Doses of Trappsol® by Measurement of Plasma Levels (Tmax)

End point title	To Evaluate the Plasma Pharmacokinetics of 3 Doses of Trappsol® by Measurement of Plasma Levels (Tmax)[3]

End point description:

To evaluate plasma PK of Trappsol® by comparison of time to maximum concentration (tmax) of the three doses

End point type	Primary

End point timeframe:

0,2,4,6,& 8 hours (h) after the start of the IV infusion of Trappsol® and 0.5,1,2,4,8 & 12 h after the end of the infusion

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: Quantitative statistical analysis was not performed for this PK endpoint. Descriptive statistics are included.

End point values	Trappsol® Cyclo™ IV 1500 mg/kg	Trappsol® Cyclo™ IV 2000 mg/kg	Trappsol® Cyclo™ IV 2500 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	3	3	
Units: hours				
arithmetic mean (standard deviation)	5.66 (± 1.7)	6.7 (± 1.16)	6.02 (± 0.03)	

Statistical analyses

No statistical analyses for this end point

Primary: To Evaluate the Plasma Pharmacokinetics of 3 Doses of Trappsol® by Measurement of Plasma Levels (Vd)

End point title	To Evaluate the Plasma Pharmacokinetics of 3 Doses of Trappsol® by Measurement of Plasma Levels (Vd)[4]

End point description:

To evaluate plasma PK of Trappsol® by comparison of volume of distribution (Vd) of the three doses

End point type	Primary

End point timeframe:

0,2,4,6,& 8 hours (h) after the start of the IV infusion of Trappsol® and 0.5,1,2,4,8 & 12 h after the end of the infusion

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: Quantitative statistical analysis was not performed for this PK endpoint. Descriptive statistics are included.

End point values	Trappsol® Cyclo™ IV 1500 mg/kg	Trappsol® Cyclo™ IV 2000 mg/kg	Trappsol® Cyclo™ IV 2500 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	3	3	
Units: ml/kg				
median (standard deviation)	426 (± 168)	399 (± 193)	412 (± 107)	

Statistical analyses

No statistical analyses for this end point

Primary: To Evaluate the Plasma Pharmacokinetics of 3 Doses of Trappsol® by Measurement of Plasma Levels (T1/2)

End point title	To Evaluate the Plasma Pharmacokinetics of 3 Doses of Trappsol® by Measurement of Plasma Levels (T1/2)[5]

End point description:

Plasma elimination half-life (T1/2)

End point type	Primary

End point timeframe:

0,2,4,6,& 8 hours (h) after the start of the IV infusion of Trappsol® and 0.5,1,2,4,8 & 12 h after the end of the infusion

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: Quantitative statistical analysis was not performed for this PK endpoint. Descriptive statistics are included.

End point values	Trappsol® Cyclo™ IV 1500 mg/kg	Trappsol® Cyclo™ IV 2000 mg/kg	Trappsol® Cyclo™ IV 2500 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	3	3	
Units: Hours				
arithmetic mean (standard deviation)	2.01 (± 0.27)	1.63 (± 0.15)	1.81 (± 0.259)	

Statistical analyses

No statistical analyses for this end point

Primary: To Evaluate the Cerebrospinal fluid (CSF) Pharmacokinetics of 3 Doses of Trappsol® (Concentration of HP-β-CD in the CSF)

End point title	To Evaluate the Cerebrospinal fluid (CSF) Pharmacokinetics of 3 Doses of Trappsol® (Concentration of HP-β-CD in the CSF)[6]

End point description:

To evaluate Concentration of HP-β-CD in the CSF of the three doses of Trappsol®

End point type	Primary

End point timeframe:

8 hour after start of 1st Infusion

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: Quantitative statistical analysis was not performed for this PK endpoint. Descriptive statistics are included.

End point values	Trappsol® Cyclo™ IV 1500 mg/kg	Trappsol® Cyclo™ IV 2000 mg/kg	Trappsol® Cyclo™ IV 2500 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	4	2	
Units: ng/mL				
arithmetic mean (full range (min-max))	232600 (22200 to 443000)	22225 (0 to 48800)	184400 (16800 to 352000)	

Statistical analyses

No statistical analyses for this end point

Primary: To Evaluate CSF to Plasma ratio of 3 doses of Trappsol®

End point title	To Evaluate CSF to Plasma ratio of 3 doses of Trappsol®[7]

End point description:

The mean ratio of CSF HP-β-CD concentration to plasma HP-β-CD concentration in the three reporting groups

End point type	Primary

End point timeframe:

0,2,4,6,& 8 hours (h) after the start of the IV infusion of Trappsol® and 0.5,1,2,4,8 & 12 h after the end of the infusion

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: Quantitative statistical analysis was not performed for this PK endpoint. Descriptive statistics are included.

End point values	Trappsol® Cyclo™ IV 1500 mg/kg	Trappsol® Cyclo™ IV 2000 mg/kg	Trappsol® Cyclo™ IV 2500 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3[8]	4[9]	3[10]	
Units: Ratio				
arithmetic mean (standard deviation)	0.215 (± 0.353)	0.0608 (± 0.124)	0.196 (± 0.157)	

Notes:

[8] - 7 samples from 3 participants

[9] - 8 samples from 4 participants

[10] - 4 samples from 3 participants

Statistical analyses

No statistical analyses for this end point

Secondary: To Evaluate the Effect of Treatment on Plasma Biomarkers of NPC disease

End point title	To Evaluate the Effect of Treatment on Plasma Biomarkers of NPC disease

End point description:

Niemann-Pick disease type C (NPC-1)

End point type	Secondary

End point timeframe:
Week 12

End point values	Across the dose range			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: % Change from baseline				
arithmetic mean (standard deviation)				
Lysosphingomyelin 509	61.3 (± 17.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: To Evaluate the Effect of Treatment on Biomarkers of Cholesterol Metabolism (Serum Lathosterol, 27-hydroxycholesterol, 24S-hydroxycholesterol)

End point title	To Evaluate the Effect of Treatment on Biomarkers of Cholesterol Metabolism (Serum Lathosterol, 27-hydroxycholesterol, 24S-hydroxycholesterol)

End point description:

End point type	Secondary

End point timeframe:
Various times post dosing (Day 3 post dose)

End point values	Across the dose range			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: Mean % of baseline				
arithmetic mean (standard deviation)				
Lathosterol	59.11 (± 13.45)			
27-hydroxycholesterol	199.19 (± 45.69)			
24S-hydroxycholesterol	117.9 (± 6.74)			

Statistical analyses

No statistical analyses for this end point

Secondary: To Evaluate the Effect of Treatment on Biomarkers of Cholesterol

Metabolism (LDL and HDL cholesterol)

End point title	To Evaluate the Effect of Treatment on Biomarkers of Cholesterol Metabolism (LDL and HDL cholesterol)

End point description:

End point type	Secondary

End point timeframe:

Various times post dosing (Day 3 post dose)

End point values	Across the dose range			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: Mmol/L				
arithmetic mean (standard deviation)				
LDL cholesterol	4.06 (± 0.83)			
HDL cholesterol	1.35 (± 0.24)			

Statistical analyses

No statistical analyses for this end point

Secondary: To Evaluate the Effect of Treatment on CSF Biomarkers of NPC disease

End point title	To Evaluate the Effect of Treatment on CSF Biomarkers of NPC disease

End point description:

End point type	Secondary

End point timeframe:

Week 48

End point values	Across the dose range			
Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: % baseline				
arithmetic mean (full range (min-max))				
CSF Tau	48.83 (28.11 to 69.56)			

Statistical analyses

No statistical analyses for this end point

Secondary: To Evaluate the Effect of Treatment on NIH NPC severity scale 17

End point title	To Evaluate the Effect of Treatment on NIH NPC severity scale 17

End point description:

NIH NPC severity scale (NCSS) (17 item) and Clinical Global Impression (CGI-I)

End point type	Secondary

End point timeframe:

NIH NPC severity scale Week 48, CGI Week 12 and Week 48

End point values	Across the dose range			
Subject group type	Subject analysis set			
Number of subjects analysed	12[11]			
Units: Mean Score				
arithmetic mean (standard deviation)				
NCSS Mean total score	17.3 (± 5.97)			
CGI-I Mean score w 12	2.9 (± 0.89)			
CGI-I Mean score End of study	2.7 (± 1.0)			

Notes:

[11] - 11 subjects analysed for CGI-I mean score

Statistical analyses

No statistical analyses for this end point

Other pre-specified: To Evaluate the Effect of Treatment on Liver and Spleen Morphology

End point title	To Evaluate the Effect of Treatment on Liver and Spleen Morphology

End point description:

Measure of organ length by ultrasound

End point type	Other pre-specified

End point timeframe:

Change from baseline to end of study

End point values	Across the dose range			
Subject group type	Subject analysis set			
Number of subjects analysed	8[12]			
Units: Cm				
arithmetic mean (standard deviation)				
Change in liver size	-0.198 (± 1.235)			
Change in spleen size	-1.22 (± 1.415)			

Notes:
[12] - 6 subjects analysed for change in spleen size

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events (AEs) were continuously monitored throughout the study from signing of the ICF until the last follow-up assessment	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Trappsol® Cyclo™ IV 1500 mg/kg
Reporting group description:	
HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks.	
Reporting group title	Trappsol® Cyclo™ IV 2000 mg/kg
Reporting group description:	
HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks.	
Reporting group title	Trappsol® Cyclo™ IV 2500 mg/kg
Reporting group description:	
HP-β-CD was administered as Trappsol® Cyclo™ 25% (250 mg/mL) diluted with normal saline as needed up to a set volume by slow IV infusion over a period of 8 to 9 hours every 2 weeks	

Serious adverse events	Trappsol® Cyclo™ IV 1500 mg/kg	Trappsol® Cyclo™ IV 2000 mg/kg	Trappsol® Cyclo™ IV 2500 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)	1 / 4 (25.00%)	2 / 3 (66.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrospinal fluid leakage			

subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Peripheral swelling			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonia aspiration			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Influenza/Influenza B			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Trappsol® Cyclo™ IV 1500 mg/kg	Trappsol® Cyclo™ IV 2000 mg/kg	Trappsol® Cyclo™ IV 2500 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	4 / 4 (100.00%)	3 / 3 (100.00%)
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	3 / 3 (100.00%)
occurrences (all)	1	0	5
Fatigue			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	1 / 3 (33.33%)
occurrences (all)	0	1	2
Peripheral Swelling			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Catheter Site Erythema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Catheter Site Rash			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Gait Disturbance			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 5 (60.00%)	1 / 4 (25.00%)	2 / 3 (66.67%)
occurrences (all)	3	2	7
Rhinorrhoea			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Epistaxis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Oropharyngeal Pain			

subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Pneumonia Aspiration			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Tonsillar Hypertrophy			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Wheezing			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Psychiatric disorders			
Mood swings			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Investigations			
Acoustic Stimulation Tests Abnormal			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	1	6	0
Blood Cholesterol Increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Body Temperature Increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
High Density Lipoprotein Decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Low Density Lipoprotein Increased			

subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Platelet Count Decreased			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Weight Decreased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
C-reactive protein increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Electrocardiogram T wave amplitude decreased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	1 / 3 (33.33%)
occurrences (all)	0	1	3
Fall			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	2
Gastrostomy Tube Site Complication			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	1 / 3 (33.33%)
occurrences (all)	0	1	5
Head Injury			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Laceration			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Post Lumbar Puncture Syndrome			

subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Procedural Pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Procedural Vomiting			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Cardiac disorders			
Pericardial Effusion			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Tachycardia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Seizure			
subjects affected / exposed	2 / 5 (40.00%)	1 / 4 (25.00%)	1 / 3 (33.33%)
occurrences (all)	2	2	3
Cataplexy			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	2	0	2
Cerebrospinal Fluid Leakage			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Amnesia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Ataxia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Dyskinesia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Headache			

subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Petit Mal Epilepsy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	2 / 3 (66.67%)
occurrences (all)	0	0	4
Restless Legs Syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Speech Disorder			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Cerumen Impaction			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Tinnitus			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Eye swelling			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 5 (20.00%)	3 / 4 (75.00%)	2 / 3 (66.67%)
occurrences (all)	3	4	5
Diarrhoea			

subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	3 / 3 (100.00%)
occurrences (all)	1	3	6
Nausea			
subjects affected / exposed	0 / 5 (0.00%)	2 / 4 (50.00%)	0 / 3 (0.00%)
occurrences (all)	0	4	0
Abdominal Distension			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Frequent Bowel Movements			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	5	0	0
Pigmentation Lip			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	1 / 3 (33.33%)
occurrences (all)	5	1	1
Erythema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Swelling face			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Incontinence			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	1 / 3 (33.33%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 5 (0.00%)	2 / 4 (50.00%)	0 / 3 (0.00%)
occurrences (all)	0	2	0
Muscle twitching			

subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 5 (60.00%)	1 / 4 (25.00%)	2 / 3 (66.67%)
occurrences (all)	4	1	3
Nasopharyngitis			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	2 / 3 (66.67%)
occurrences (all)	1	2	3
Rhinitis			
subjects affected / exposed	2 / 5 (40.00%)	1 / 4 (25.00%)	1 / 3 (33.33%)
occurrences (all)	2	4	6
Tonsillitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Viral Infection			
subjects affected / exposed	1 / 5 (20.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	1	1	0
Anal Fungal Infection			
subjects affected / exposed	1 / 5 (20.00%)	0 / 4 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Skin infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Urinary Tract Infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 4 (25.00%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	0 / 5 (0.00%)	0 / 4 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 July 2016	Version 2.0 Removal of VFSE; correction to Figure 1 Study Schematic; correction of NCCS to NCSS; AE causality changed from yes/no to unlikely, possibly, probably; neurology testing and PBMCs added to Day 1 in Table of Assessments
06 September 2016	Version 2.1 Expanded definition of effective contraception in exclusion criterion 11; exclusion criterion 12 added breastfeeding females; discontinuation criteria for CTCAE G3 ototoxicity and CTCAE G3 renal failure added; change of "expected adverse events" to observed and SUSAR requirements added; emergency unblinding process added
18 October 2016	Version 3.0, Protocol amendment 1 Updated as per SA1
09 May 2018	Version 4.0, Protocol amendment 2 All NSA2 and SA2 changes added
21 November 2019	Version 5.0, Protocol amendment 3 SWE - Addition of interim analysis; change to EU representative; IB version 4.0; change of company name from CTD Holdings to Cyclo Therapeutics, Inc.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported