Clinical trial results:
A Brain Imaging and Cognition Study to Determine Changes in Cerebral Perfusion and Cognition After Oral Administration of CST-103 or CST-139

Summary

EudraCT number	2020-003796-17
Trial protocol	GB
Global end of trial date	29 October 2021

Results information

Result version number	v1 (current)
This version publication date	11 October 2022
First version publication date	11 October 2022

Trial information

Trial identification

Sponsor protocol code	CST103/CST139-CLIN-010

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	CuraSen Therapeutics, Inc.
Sponsor organisation address	930 Brittan Avenue, #306, San Carlos, United States, CA94070
Public contact	Clinical Trial Information Desk, CuraSen Therapeutics, Inc., +1 650475 2842, clinicaltrials@curasen.com
Scientific contact	Clinical Trial Information Desk, CuraSen Therapeutics, Inc., +1 650475 2842, clinicaltrials@curasen.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	14 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 October 2021
Global end of trial reached?	Yes
Global end of trial date	29 October 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study are:
Part A:
To evaluate the effects of CST-139 on cerebral perfusion in healthy subjects.
Part B:
To evaluate the effects of multiple doses of CST-139 on cerebral perfusion in subjects with Mild Cognitive Impairment (MCI) or Parkinson's Disease (PD).
Part C:
To evaluate the effects of multiple doses of CST-103 on cognition in subjects with MCI or PD.
Part D:
To evaluate the effects of multiple doses of CST-103 on cognition in older healthy subjects (aged 55 to 75 years)
Part E:
To evaluate the effects of a single dose of CST-103 on cerebral perfusion in subjects who completed Part C or D

Protection of trial subjects:

Written informed consent was obtained from each subject before any investigation specifically required for the study was performed. The informed consent forms (ICFs) were signed and dated, and were retained by the Principal Investigator as part of the clinical trial records. The terms of the consent and when it was obtained was also documented in the electronic case report form (eCRF). Each subject received a fully signed copy of each ICF that he/she signed for the study.
If a protocol amendment had substantially altered the clinical trial design or increased potential risk to the study subjects, the ICF would have been revised and, if applicable, the subject's consent to continue participation obtained.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 November 2020
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	United Kingdom: 34
Worldwide total number of subjects	34
EEA total number of subjects	0

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)	29
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects who gave informed consent were screened for the study between Day -21 and Day -1. Subjects who met the eligibility criteria were enrolled and underwent the baseline assessments.

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Part A - CST-139 2mg

Arm description:

Healthy volunteers enrolled in Part A who received CST-139 2 mg

Arm type	Experimental
Investigational medicinal product name	CST-139
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The study drug was administered as two or four 1-mg CST-139 tablets twice daily (4 hours apart) in the clinical study unit by the Investigator or trained and qualified designee. The first dose of study drug was administered on Day 1 following an overnight fast and light breakfast and the second dose was administered 4 hours after the first dose.

Arm title	Part A - CST-139 4 mg

Arm description:

Healthy volunteers enrolled to Part A who received 4 mg CST-139.

Arm type	Experimental
Investigational medicinal product name	CST-139
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The study drug was administered as two or four 1-mg CST-139 tablets twice daily (4 hours apart) in the clinical study unit by the Investigator or trained and qualified designee. The first dose of study drug was administered on Day 1 following an overnight fast and light breakfast and the second dose was administered 4 hours after the first dose.

Arm title	Part C - Placebo

Arm description:

Patients with Parkinson's disease (PD) enrolled into Part C following treatment with placebo.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects were randomised to received active vs placebo in a cross-over design involving a 7 day dosing period, followed by a 14 day washout, followed by cross-over to 7 days dosing with the other treatment. The study drug was administered as two 40-µg CST-103 capsules or two matching placebo capsules once daily. Study drug was administered in the clinical study unit by the Investigator or trained and qualified designee following an overnight fast and light breakfast on Days 1 and 7 of each treatment period. On Days 2 to 6, the doses were self-administered by the subjects at home.

Arm title	Part C - CST-103 80 µg

Arm description:

Patients with Parkinson's Disease enrolled in Part C following treatment with CST-103.

Arm type	Experimental
Investigational medicinal product name	CST-103 80 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects were randomised to received active vs placebo in a cross-over design involving a 7 day dosing period, followed by a 14 day washout, followed by cross-over to 7 days dosing with the other treatment. The study drug was administered as two 40-µg CST-103 capsules or two matching placebo capsules once daily. Study drug was administered in the clinical study unit by the Investigator or trained and qualified designee following an overnight fast and light breakfast on Days 1 and 7 of each treatment period. On Days 2 to 6, the doses were self-administered by the subjects at home.

Arm title	Part D - Placebo

Arm description:

Healthy volunteers enrolled in Part D following treatment with placebo.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects were randomised to received active vs placebo in a cross-over design involving a 7 day dosing period, followed by a 14 day washout, followed by cross-over to 7 days dosing with the other treatment. The study drug was administered as two 40-µg CST-103 capsules or two matching placebo capsules once daily. Study drug was administered in the clinical study unit by the Investigator or trained and qualified designee following an overnight fast and light breakfast on Days 1 and 7 of each treatment period. On Days 2 to 6, the doses were self-administered by the subjects at home.

Arm title	Part D - CST-103 80 µg

Arm description:

Healthy volunteers enrolled in Part D following treatment with CST-103.

Arm type	Experimental
Investigational medicinal product name	CST-103 80 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects were randomised to received active vs placebo in a cross-over design involving a 7 day dosing

period, followed by a 14 day washout, followed by cross-over to 7 days dosing with the other treatment. The study drug was administered as two 40-µg CST-103 capsules or two matching placebo capsules once daily. Study drug was administered in the clinical study unit by the Investigator or trained and qualified designee following an overnight fast and light breakfast on Days 1 and 7 of each treatment period. On Days 2 to 6, the doses were self-administered by the subjects at home.

Arm title	Part E - CST-103 80 µg

Arm description:

Healthy volunteers who completed Part D, enrolled to Part E and received CST-103.

Arm type	Experimental
Investigational medicinal product name	CST-103 80 µg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The study drug was administered by the Investigator or trained and qualified designee as two 40-µg CST-103 capsules in the clinical study unit following an overnight fast and light breakfast on Day 1.

Number of subjects in period 1	Part A - CST-139 2mg	Part A - CST-139 4 mg	Part C - Placebo
Started	5	6	6
Completed	5	5	6
Not completed	0	1	0
Adverse event, non-fatal	-	1	-

Number of subjects in period 1	Part C - CST-103 80 µg	Part D - Placebo	Part D - CST-103 80 µg
Started	7	16	16
Completed	6	16	16
Not completed	1	0	0
Adverse event, non-fatal	1	-	-

Number of subjects in period 1	Part E - CST-103 80 µg
Started	8
Completed	8
Not completed	0
Adverse event, non-fatal	-

Baseline characteristics

Reporting groups	
Reporting group title	Overall study

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	34	34	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	29	29	
From 65-84 years	5	5	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	14	14	
Male	20	20	

End points

End points reporting groups

Reporting group title	Part A - CST-139 2mg
Reporting group description:	
Healthy volunteers enrolled in Part A who received CST-139 2 mg	
Reporting group title	Part A - CST-139 4 mg
Reporting group description:	
Healthy volunteers enrolled to Part A who received 4 mg CST-139.	
Reporting group title	Part C - Placebo
Reporting group description:	
Patients with Parkinson's disease (PD) enrolled into Part C following treatment with placebo.	
Reporting group title	Part C - CST-103 80 µg
Reporting group description:	
Patients with Parkinson's Disease enrolled in Part C following treatment with CST-103.	
Reporting group title	Part D - Placebo
Reporting group description:	
Healthy volunteers enrolled in Part D following treatment with placebo.	
Reporting group title	Part D - CST-103 80 µg
Reporting group description:	
Healthy volunteers enrolled in Part D following treatment with CST-103.	
Reporting group title	Part E - CST-103 80 µg
Reporting group description:	
Healthy volunteers who completed Part D, enrolled to Part E and received CST-103.	

Primary: Part A: Change in cerebral perfusion (am)

End point title	Part A: Change in cerebral perfusion (am)[1][2]
End point description:	
The change in cerebral perfusion after oral administration of CST-139 as measured by arterial spin labeling magnetic resonance imaging (ALD MRI) in healthy subjects.	
End point type	Primary
End point timeframe:	
Change from Baseline to 3 hours (± 30-minute window) after administration of the morning dose.	

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: As per protocol, no statistical analyses were performed.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per protocol, this end point was relevant to Part A only.

End point values	Part A - CST-139 2mg	Part A - CST-139 4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	2		
Units: Percentage				
arithmetic mean (standard deviation)				
Whole grey matter	0.95 (± 3.77)	-4.05 (± 3.13)		
Cortex	0.48 (± 3.93)	-3.95 (± 2.99)		
Subcortical	6.04 (± 5.55)	4.26 (± 3.82)		

Striatum	6.03 (± 5.73)	7.06 (± 3.61)		
Thalamus	6.38 (± 6.02)	-2.44 (± 3.67)		
Amygdala	6.47 (± 10.69)	4.84 (± 10.90)		
Hippocampus	7.29 (± 7.34)	5.95 (± 4.46)		
Cerebellum	2.26 (± 4.26)	-6.89 (± 4.45)		
Whole white matter	0.37 (± 3.87)	-4.59 (± 2.95)		

Statistical analyses

No statistical analyses for this end point

Primary: Part A: Change in cerebral perfusion (pm)

End point title	Part A: Change in cerebral perfusion (pm)[3][4]

End point description:

The change in cerebral perfusion after oral administration of CST-139 as measured by arterial spin labeling magnetic resonance imaging (ALD MRI) in healthy subjects.

End point type	Primary

End point timeframe:

Change from Baseline to 3 hours (± 30-minute window) after administration of the afternoon 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: As per protocol, no statistical analyses were performed.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per protocol, this end point was relevant to Part A only.

End point values	Part A - CST-139 2mg	Part A - CST-139 4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	2		
Units: Percentage				
arithmetic mean (standard deviation)				
Whole grey matter	5.18 (± 7.06)	3.01 (± 4.44)		
Cortex	4.12 (± 7.38)	2.09 (± 4.45)		
Subcortical	11.20 (± 7.38)	6.45 (± 4.00)		
Striatum	9.61 (± 7.76)	4.78 (± 3.39)		
Thalamus	14.18 (± 7.86)	9.00 (± 5.12)		
Amygdala	10.66 (± 8.02)	8.07 (± 2.08)		
Hippocampus	13.11 (± 5.48)	11.69 (± 2.85)		
Cerebellum	9.42 (± 7.51)	7.28 (± 3.82)		
Whole white matter	4.72 (± 4.94)	1.79 (± 3.58)		

Statistical analyses

No statistical analyses for this end point

Primary: Part C: Change in CANTAB cognitive assessments

End point title	Part C: Change in CANTAB cognitive assessments[5][6]

End point description:

CANTAB Connect is a standardised and automated administration of cognitive testing via touch tablet, which includes the following assessments:
- Reaction Time (RTI) task
- Immediate and delayed Verbal Recognition Memory (VRM) recall and recognition tests
- Adaptive Tracking Task (ATT)
- Paired Associates Learning (PAL) task

End point type	Primary

End point timeframe:

Change from Baseline to Day 7, 3 hrs post-dose.

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: As per protocol, no statistical analyses were performed.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per protocol, this end point was relevant to Part C only.

End point values	Part C - Placebo	Part C - CST-103 80 µg	Part D - Placebo	Part D - CST-103 80 µg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	16	16
Units: Counts				
arithmetic mean (standard deviation)				
ATT Euclidean Distance Mean	-1.37 (± 3.390)	0.16 (± 6.717)	-0.16 (± 1.384)	-1.67 (± 1.561)
ATT Euclidean Distance Standard Deviation	2.47 (± 1.956)	6.80 (± 10.165)	2.62 (± 4.013)	1.88 (± 3.406)
ATT Difficulty Multiplier Mean	0.22 (± 0.317)	0.20 (± 0.397)	0.19 (± 0.165)	0.27 (± 0.115)
ATT Difficulty Multiplier Standard Deviation	0.04 (± 0.026)	0.07 (± 0.124)	0.04 (± 0.055)	0.05 (± 0.054)
RTI Median 5-Choice Movement Time	-24.08 (± 51.868)	-18.00 (± 57.546)	-11.06 (± 27.919)	-11.16 (± 42.054)
RTI Median 5-Choice Reaction Time	-15.92 (± 43.496)	-9.08 (± 24.824)	-13.66 (± 36.870)	-22.94 (± 36.446)
PAL First Attempt Memory Score	1.5 (± 2.07)	1.5 (± 4.04)	0.6 (± 4.23)	0.1 (± 4.77)
PAL Number of Patterns Reached	0.3 (± 0.82)	0.3 (± 0.82)	0.3 (± 1.24)	0.3 (± 1.00)
PAL Total Errors (Adjusted)	-3.5 (± 11.33)	-4.5 (± 11.24)	-4.1 (± 12.15)	-4.0 (± 11.45)
VRM Free Recall Distinct Stimuli - P1.1	0.2 (± 3.06)	-0.2 (± 2.56)	-0.1 (± 3.19)	-0.6 (± 3.41)
VRM Free Recall Distinct Stimuli - P1.2	0.5 (± 3.39)	-0.8 (± 2.23)	-0.6 (± 2.45)	0.1 (± 2.43)
VRM Free Recall Distinct Stimuli - P1.3	-0.7 (± 1.86)	0.2 (± 1.47)	-1.3 (± 2.98)	-0.9 (± 2.77)
VRM Delayed Free Recall Distinct Stimuli - P2.1	0.6 (± 3.36)	0.2 (± 3.31)	-1.5 (± 2.50)	-1.1 (± 3.10)
VRM Delayed Recognition Total Correct - P2.2	-0.6 (± 2.30)	0.0 (± 2.10)	-1.0 (± 1.83)	-0.5 (± 1.59)

Statistical analyses

No statistical analyses for this end point

Primary: Part E: Change in cerebral perfusion

End point title	Part E: Change in cerebral perfusion[7][8]

End point description:

The change in cerebral perfusion after oral administration of CST-103 as measured by arterial spin labeling magnetic resonance imaging (ALD MRI) in healthy subjects.

End point type	Primary

End point timeframe:

Change from Baseline to 3 hours (± 60-minute window) post-dose.

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: As per protocol, no statistical analyses were performed.

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Per protocol, this end point was relevant to Part E only.

End point values	Part E - CST-103 80 µg			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Percentage				
arithmetic mean (standard deviation)				
Whole grey matter	4.76 (± 5.44)			
Cortex	3.86 (± 5.03)			
Subcortical	8.90 (± 4.81)			
Striatum	5.83 (± 6.41)			
Thalamus	15.24 (± 8.00)			
Amygdala	9.96 (± 6.96)			
Hippocampus	21.73 (± 8.89)			
Cerebellum	8.46 (± 9.83)			
Whole white matter	5.67 (± 6.42)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose until completion of end of study visit.

Adverse event reporting additional description:

It is noted that the number of occurrences of each adverse event was not reported in the Clinical Study Report. Therefore the number of occurrences presented below is the same as the number of subjects experiencing each event.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Part A - CST-139 2mg

Reporting group description:

Healthy volunteers enrolled in Part A who received CST-139 2 mg

Reporting group title	Part A - CST-139 4 mg

Reporting group description:

Healthy volunteers enrolled to Part A who received 4 mg CST-139.

Reporting group title	Part C - Placebo

Reporting group description:

Patients with Parkinson's disease (PD) enrolled into Part C and randomised to receive placebo.

Reporting group title	Part C - CST-103

Reporting group description:

Patients with Parkinson's Disease enrolled in Part C and randomised to receive CST-103

Reporting group title	Part D - Placebo

Reporting group description:

Healthy volunteers enrolled in Part D and randomised to receive placebo.

Reporting group title	Part D - CST-103

Reporting group description:

Healthy volunteers enrolled in Part D randomised to receive CST-103.

Reporting group title	Part E - CST-103

Reporting group description:

Patients with Parkinson's disease who completed Part C or Part D, enrolled to Part E and received CST-103.

Serious adverse events	Part A - CST-139 2mg	Part A - CST-139 4 mg	Part C - Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Part C - CST-103	Part D - Placebo	Part D - CST-103
Total subjects affected by serious			

adverse events			
subjects affected / exposed	0 / 7 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Part E - CST-103		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Part A - CST-139 2mg	Part A - CST-139 4 mg	Part C - Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 5 (80.00%)	2 / 6 (33.33%)	2 / 6 (33.33%)
Investigations			
Electrocardiogram ST segment depression			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 5 (40.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
Palpitations			
subjects affected / exposed	1 / 5 (20.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 5 (60.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	3	2	0
Tremor			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dizziness			

subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Feeling jittery			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Feeling abnormal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Otorrhoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Toothache			
subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dry mouth			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Nervousness			
subjects affected / exposed	0 / 5 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Pollakiuria			

subjects affected / exposed	1 / 5 (20.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Muscle tightness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Oral herpes			
subjects affected / exposed	0 / 5 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 6 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0

Non-serious adverse events	Part C - CST-103	Part D - Placebo	Part D - CST-103
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 7 (71.43%)	5 / 16 (31.25%)	13 / 16 (81.25%)
Investigations			
Electrocardiogram ST segment depression			
subjects affected / exposed	0 / 7 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			

Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Palpitations			
subjects affected / exposed	2 / 7 (28.57%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	2	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 7 (42.86%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	3	1	0
Tremor			
subjects affected / exposed	4 / 7 (57.14%)	0 / 16 (0.00%)	9 / 16 (56.25%)
occurrences (all)	4	0	9
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Feeling jittery			
subjects affected / exposed	0 / 7 (0.00%)	0 / 16 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	2
Fatigue			
subjects affected / exposed	0 / 7 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Feeling abnormal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Otorrhoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Toothache			
subjects affected / exposed	0 / 7 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Dry mouth			

subjects affected / exposed	1 / 7 (14.29%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Nervousness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 7 (14.29%)	0 / 16 (0.00%)	4 / 16 (25.00%)
occurrences (all)	1	0	4
Muscle tightness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 16 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 16 (0.00%)	0 / 16 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	0 / 7 (0.00%)	1 / 16 (6.25%)	0 / 16 (0.00%)
occurrences (all)	0	1	0

Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 16 (0.00%)	2 / 16 (12.50%)
occurrences (all)	0	0	2

Non-serious adverse events	Part E - CST-103		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 8 (50.00%)		
Investigations			
Electrocardiogram ST segment depression			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Palpitations			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Dizziness			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
General disorders and administration site conditions			
Feeling jittery			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Feeling abnormal			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Ear and labyrinth disorders Otorrhoea subjects affected / exposed occurrences (all)	 0 / 8 (0.00%) 0		
Gastrointestinal disorders Toothache subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0		
Psychiatric disorders Nervousness subjects affected / exposed occurrences (all)	 0 / 8 (0.00%) 0		
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	 0 / 8 (0.00%) 0		
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) Muscle tightness subjects affected / exposed occurrences (all) Myalgia	 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0		

subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0 1 / 8 (12.50%) 1		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) Oral herpes subjects affected / exposed occurrences (all)	 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	 0 / 8 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 October 2020	The major changes in Version 2.0 (Amendment 1, 07 October 2020) were: • Added a section describing the Dose Level Review Meetings (DLRMs). • Revised the contraceptive inclusion criteria to reference the added Section 5.5, Contraception based on comments from the Medicines and Healthcare products Regulatory Agency (MHRA). Changes were inclusion of a definition of sexual abstinence, removal of period abstinence and withdrawal as acceptable methods of contraception, and removal of tubal ligation as a surgical sterilization procedure. • Added the exclusion criterion regarding uncontrolled hypertension based on comments from the MHRA because β-AR agonists are known to be associated with hypertension risk. • For clarity, revised terminology "Q4 hours" to specify that twice-daily doses were to be given 4 hours apart.
26 January 2021	The major changes in Versions 3.0, 3.1 and 3.2 (Amendment 2, 20 January 2021, 21 January 2021 and 26 January 2021, respectively) were: • Changed the primary objective of Part C to evaluating the effects of multiple doses of CST-103 on cognition (it was previously cerebral perfusion based on imaging) and changed the design so that the same randomized, double-blind, placebo-controlled, 2-way crossover design would be used in Parts C and D. Part C was originally designed to provide both imaging and cognition data on the same subjects. However, to minimize potential COVID-19 exposure that may have occurred during the imaging procedure, the protocol was amended to remove imaging during the worst of the COVID-19 pandemic. • Added Part D to evaluate the effects of multiple doses of CST-103 on cognition in older healthy subjects. • Deleted the exclusion criterion for subjects on monoamine oxidase type B inhibitors, dopamine agonists, or catechol-O-methyltransferase inhibitors. Those medications are commonly used by Parkinson's Disease (PD) subjects and were not excluded in other CuraSen studies in a similar study population.
26 April 2021	The major changes in Versions 4.0 and 4.1 (Amendment 3, 22 April 2021 and 26 April 2021, respectively), which was the final version of the protocol, were: • Deleted Part B that was to evaluate the effects of multiple doses of CST-139 on cerebral perfusion in subjects with Mild Cognitive Impairment (MCI) or PD. A DLRM meeting after the conclusion of Part A determined that due to the drug-related Treatment-Emergent Adverse Events (TEAEs) and variability in the CST-139 plasma concentrations and pharmacokinetics results further investigation of CST-139 in Part B was not warranted. • Added Part E to evaluate the effects of a single dose of CST-103 on cerebral perfusion in subjects who completed Parts C or D.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
02 September 2021	The study was placed on temporary hold and then subsequently terminated early due to a high screen failure rate, challenges due to the COVID-19 pandemic, and a competing CuraSen study enrolling subjects at the same site. There were no safety concerns with the program.	-

Notes:

Limitations and caveats

None reported