Clinical trial results:
A Pilot Electroencephalography (EEG) Study to Evaluate the Effect of CT1812 Treatment on Synaptic Activity in Subjects With Mild to Moderate Alzheimer's Disease

Summary

EudraCT number	2019-003552-36
Trial protocol	NL
Global end of trial date	26 April 2023

Results information

Result version number	v1 (current)
This version publication date	10 May 2024
First version publication date	10 May 2024

Trial information

Trial identification

Sponsor protocol code	COG0202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04735536
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cognition Therapeutics
Sponsor organisation address	2500 Westchester Ave suite 220, Purchase,NY, United States, 10577
Public contact	Chief Medical Officer, Head of R&D, acaggiano@cogrx.com, +1 9142216730, acaggiano@cogrx.com
Scientific contact	Chief Medical Officer, Head of R&D, Cognition Therapeutics, +31 0203017170, j.vijverberg@brainresearchcenter.nl

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 June 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 April 2023
Global end of trial reached?	Yes
Global end of trial date	26 April 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study was designed to identify measures of target engagement that reflect the rapid mechanism of action of CT1812 to restore synapse number to normal. The ability of CT1812 to rapidly restore synapse number to normal was expected to result in a decrease in EEG theta power. Primary objectives:
• To evaluate the safety, tolerability, and pharmacokinetics (PK) of CT1812 following repeated dosing of CT1812 for 29 days.
• To evaluate the efficacy of CT1812 in restoring synaptic function in participants with mild to moderate AD through quantitative EEG measurements, as reflected by relative theta power.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. This study was conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), including the archiving of essential documents. A study safety monitoring committee oversaw the safety of the study. This committee included the study director, the Sponsor’s medical monitor, and the site’s principal Investigator. Safety data (lab reports, AEs) were provided to the safety committee to review at monthly intervals during the study. The committee met approximately once quarterly to discuss study safety data.

Background therapy:

Participants were excluded from the study if this criterion related to background therapy was met: Within 4 weeks of screening visit or during the study, concurrent treatment with antipsychotic agents, antiepileptics, centrally active anti-hypertensive drugs (e.g., clonidine, l-methyl dopa, guanidine, guanfacine, etc.), sedatives, opioids, mood stabilizers (e.g., valproate, lithium); or benzodiazepines, with the following exception:
a) Low dose lorazepam may be used for sedation prior to MRI scan for those participants requiring sedation. At the discretion of the Investigator, 0.5 to 1 mg may be given orally prior to scan with a single repeat dose given if the first dose is ineffective. No more than a total of 2 mg lorazepam may be used for the MRI scan.

Evidence for comparator:

Participants received CT1812 and placebo in a double-blind cross-over design. The placebo was given to account for the placebo effect.

Actual start date of recruitment	06 January 2020
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	Netherlands: 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)	6
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at a single site in the Netherlands. Advertisements (in Dutch) for recruitment were approved by Independent Ethics Committee on 17 January 2020.

Pre-assignment

Screening details:

Screening was performed within 42 days prior to Baseline (Day 1). Some procedures: - Obtain signed Informed Consent Form - Perform 12-lead ECG - Draw blood: serum chemistry, hematology; viral serology; HbA1c in known diabetics; and TSH. Once screening results indicate participant is eligible for the or the study, the participant went through LP.

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

Blinding implementation details:

The study was a double-blind, placebo-controlled study. Study treatments consisted of capsules of CT1812 and matching placebo. The placebo capsules were identical in appearance to the active CT1812 capsules.
The unblinded statistician assigned to the study generated a list with the appropriate number of 4-digit individual participant IDs randomly assigned to Sequence 1 (CT1812 in Period 1 and placebo in Period 2) or to Sequence 2 (placebo in Period 1 and CT1812 in Period 2).

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

One group received 29 days of treatment with 300 mg of CT1812 (Period 1) and 29 days treatment with placebo (Period 2). The participants in the second group received placebo for 29 days (Period 1) and 300 mg of CT1812 for 29 days (Period 2). A 14-day washout period separated treatment Periods 1 and 2. A total of 15 participants completed the study as planned. One participant withdrew consent before being assigned to Period 2- Placebo group.

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:

Placebo capsules were to be administered orally as a single daily dose for 29 days. Capsules were swallowed with approximately 240 mL of water with or without food.

Arm title	CT1812

Arm description:

One group received 29 days of treatment with 300 mg of CT1812 (Period 1) and 29 days treatment with placebo (Period 2). The participants in the second group received placebo for 29 days (Period 1) and 300 mg of CT1812 for 29 days (Period 2). A 14-day washout period separated treatment Periods 1 and 2. All participants completed the study for the CT1812 arm (8 participants for each period 1 and 2 - 16 total).

Arm type	Experimental

Investigational medicinal product name	CT1812
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The treatments administered in this study were CT1812 300 mg and matching placebo. CT1812 or matching placebo capsules were to be administered orally as a single daily dose for 29 days. Each dose CT1812 or matching placebo consisted of 2 capsules. All participants ingested the first dose at the study site and were observed for 2 hours. Capsules were swallowed with approximately 240 mL of water with or without food.
Sequence CT1812/Placebo
Period 1:
(Days 1-29): CT1812: 300 mg - 2 capsules (150 mg/capsule) AND Placebo 2 capsules

Sequence Placebo/CT1812
Period 2
(Days 44-72): Placebo 2 capsules AND CT1812: 300 mg - 2 capsules (150 mg/capsule)

Number of subjects in period 1	Placebo	CT1812
Started	15	16
Completed	15	16

Baseline characteristics

Reporting groups	
Reporting group title	overall trial (overall period)

Reporting group description: -

Reporting group values	overall trial (overall period)	Total	
Number of subjects	16	16	
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)	6	6	
From 65-84 years	10	10	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	66.4		
standard deviation	± 7.90	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	8	8	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Black or African American	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
White	16	16	
Other	0	0	
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	16	16	
Not Reported	0	0	
Unknown	0	0	
Height (cm) at Screening Units: cm			
arithmetic mean	174.5		
standard deviation	± 10.17	-	
Weight at Screening			

Units: kg			
arithmetic mean	79.23		
standard deviation	± 16.973	-	
Body Mass Index at Screening			
Units: kg/m2			
arithmetic mean	25.910		
standard deviation	± 4.1226	-	

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

One group received 29 days of treatment with 300 mg of CT1812 (Period 1) and 29 days treatment with placebo (Period 2). The participants in the second group received placebo for 29 days (Period 1) and 300 mg of CT1812 for 29 days (Period 2). A 14-day washout period separated treatment Periods 1 and 2. A total of 15 participants completed the study as planned. One participant withdrew consent before being assigned to Period 2- Placebo group.

Reporting group title	CT1812

Reporting group description:

One group received 29 days of treatment with 300 mg of CT1812 (Period 1) and 29 days treatment with placebo (Period 2). The participants in the second group received placebo for 29 days (Period 1) and 300 mg of CT1812 for 29 days (Period 2). A 14-day washout period separated treatment Periods 1 and 2. All participants completed the study for the CT1812 arm (8 participants for each period 1 and 2 - 16 total).

Primary: Number of TEAEs, Related TEAEs, SAEs, and Related SAEs

End point title	Number of TEAEs, Related TEAEs, SAEs, and Related SAEs[1]

End point description:

Adverse events were captured from the start of study-related procedures at Visit 1 (including diagnostic assessments or signing of ICF) onward during the course of this study. Adverse events were coded using MedDRA Version 22.0

End point type	Primary

End point timeframe:

Days -42 to -1 (Screening) through Day 84

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: For TEAEs, related TEAEs, SAEs, and related SAEs: these data were not statistically analyzed – they were only summarized descriptively.

End point values	Placebo	CT1812		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[2]	16[3]		
Units: Participants				
All TEAEs	6	11		
Mild TEAEs	4	7		
Moderate TEAEs	2	4		
Severe TEAEs	0	0		
Related TEAEs	3	3		
TEAEs Leading to Treatment Discontinuation	0	0		
SAEs	0	0		
Related SAEs	0	0		

Notes:

[2] - 15 subjects were in the placebo arm (Period 1 and 2). Table shows the results for the 15 subjects.

[3] - 16 subjects were in the placebo arm (Period 1 and 2). Table shows the results for the 16 subjects.

Statistical analyses

No statistical analyses for this end point

Primary: Change in the Quantitative Electroencephalography (EEG) Measurements, as Reflected by Relative Theta Power.

End point title	Change in the Quantitative Electroencephalography (EEG) Measurements, as Reflected by Relative Theta Power.

End point description:

The primary efficacy variable, change from period baseline in global relative theta power within each period was analyzed using a linear mixed model with fixed effects for treatment group (CT1812 or placebo), sequence, and period, and a random effect for subject within sequence.

End point type	Primary

End point timeframe:

Day 1 through Day 29 (Period 1) and Day 44 through Day 72 (Period 2)

End point values	Placebo	CT1812		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15[4]	16[5]		
Units: uV2/Hz				
arithmetic mean (standard deviation)				
Period Day 1	0.2133 (± 0.06158)	0.2071 (± 0.08209)		
Period Day 29	0.2276 (± 0.07872)	0.1971 (± 0.07569)		
Change from Period Day 1	0.0104 (± 0.03210)	-0.0100 (± 0.04280)		

Notes:

[4] - 15 subjects were in the placebo arm (Period 1 and 2). Table shows the results for the 15 subjects.

[5] - 16 subjects were in the CT1812 arm (Period 1 and 2). Table shows the results for the 16 subjects.

Statistical analyses

Statistical analysis title	Between treatment analysis
Comparison groups	CT1812 v Placebo
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.123
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.0206
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0476
upper limit	0.0063
Variability estimate	Standard error of the mean
Dispersion value	0.01257

Notes:

[6] - It is noted that the number of subjects in this analysis was 16 and not 31 as automatically imputed by EudraCT.

Primary: Changes in Predose CT1812 Plasma Concentrations

End point title	Changes in Predose CT1812 Plasma Concentrations[7][8]

End point description:

For the measurements of pre-dose and post-dose plasma concentrations of CT1812, samples were collected 1± 0.25 hour predose. Single concentrations of CT1812 at selected predose and post-dose time points were reported.
The PK data were not statistically analyzed; instead, these data were summarized descriptively.

End point type	Primary

End point timeframe:

Baseline through Day 84

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: The PK data were not statistically analyzed; instead, these data were summarized descriptively.
[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: The PK data were not statistically analyzed; instead, these data were summarized descriptively.

End point values	CT1812			
Subject group type	Reporting group			
Number of subjects analysed	16[9]			
Units: ng/mL				
arithmetic mean (standard deviation)				
Period Day 1, Predose	0.00 (± 0.000)			
Period Day 1, Post-dose	179.64 (± 136.717)			
Period Day 8, Predose	25.49 (± 25.017)			
Period Day 15, Predose	14.93 (± 7.826)			
Period Day 22, Predose	13.76 (± 8.000)			
Period Day 29, Predose	14.08 (± 8.984)			
Period Day 29, Post-dose	169.20 (± 246.150)			

Notes:

[9] - 16 subjects were in the CT1812 arm (Period 1 and 2). Table shows the results for the 16 subjects.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 126 days	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22
Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	CT1812
Reporting group description: -	

Serious adverse events	Placebo	CT1812	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Placebo	CT1812	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 15 (40.00%)	11 / 16 (68.75%)	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Hepatic enzyme increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Burns first degree			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	

Bone contusion			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Post procedural contusion			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Procedural headache			
subjects affected / exposed	1 / 15 (6.67%)	3 / 16 (18.75%)	
occurrences (all)	1	3	
Vascular disorders			
Hematoma			
subjects affected / exposed	1 / 15 (6.67%)	2 / 16 (12.50%)	
occurrences (all)	1	2	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 15 (0.00%)	2 / 16 (12.50%)	
occurrences (all)	0	2	
Paraesthesia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	1 / 15 (6.67%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Nausea			
subjects affected / exposed	1 / 15 (6.67%)	2 / 16 (12.50%)	
occurrences (all)	1	2	
Vomiting			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Pneumonia			

subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Corona virus infection			
subjects affected / exposed	1 / 15 (6.67%)	1 / 16 (6.25%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 February 2022	Section: p7, 40- Inclusion Criteria Old text: CSF positive for amyloid beta (as defined in the study manual). Historical CSF results will be considered provided the results are consistent with the CSF amyloid beta threshold required for inclusion and following discussion with the medical monitor; however, an LP is still required as part of screening procedures. New text: 2) CSF abeta and tau consistent with a diagnosis of Alzheimer's disease i.e. CSF abeta 142 < 1000pg/ml (Elecsys assay) AND CSF ptau 181 > 19 pg/ml (Elcsys Assay). If one of these analytes meets the defined threshold criterion and the other analyte is close to the defined threshold criterion, a ptau 181 / abeta 142 ratio > 0.020 may be utilized to confirm eligibility, which is detailed below. Historical CSF results will be considered provided the results are consistent with the required CSF abeta and tau criteria for inclusion and following discussion with the medical monitor; however, an LP is still required as part of the screening procedures. CSF abeta 142 < 1000pg/ml (Elecsys assay) AND CSF ptau 181 > 19 pg/ml (Elcsys Assay) OR: CSF abeta 142 < 1000pg/ml (Elecsys assay) AND ptau 181 / abeta 142 ratio > 0.020 OR: CSF ptau 181 > 19 pg/ml (Elcsys Assay) AND ptau 181 / abeta 142 ratio > 0.020 Section: Pg 71 Columbia Suicide Severity Rating Scale Old text: All subsequent visits New text: Visits 2, 7, 8, and 13. Rationale: To clarify at which visits this assessment is administered Section: Pg 5 Exploratory: Cerebrospinal Fluid Old text: N/A New text: Evaluate additional quantitative EEG measures that have shown promise as diagnostic/treatment marker: relative alpha (8-13 Hz) and beta (13-30 Hz) power, theta/alpha power ratio, spectral peak frequency, and functional connectivity measures corrected Amplitude Envelope Correlation (AEC-c). Rationale: To include all exploratory endpoints in the summary

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported