



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

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: $\mu\text{V}^2/\text{Hz}$ | | | | |
| arithmetic mean (standard deviation) | | | | |
| Period Day 1 | 0.2133 (\pm 0.06158) | 0.2071 (\pm 0.08209) | | |
| Period Day 29 | 0.2276 (\pm 0.07872) | 0.1971 (\pm 0.07569) | | |
| Change from Period Day 1 | 0.0104 (\pm 0.03210) | -0.0100 (\pm 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 (\pm 0.000) | | | |
| Period Day 1, Post-dose | 179.64 (\pm 136.717) | | | |
| Period Day 8, Predose | 25.49 (\pm 25.017) | | | |
| Period Day 15, Predose | 14.93 (\pm 7.826) | | | |
| Period Day 22, Predose | 13.76 (\pm 8.000) | | | |
| Period Day 29, Predose | 14.08 (\pm 8.984) | | | |
| Period Day 29, Post-dose | 169.20 (\pm 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 occurrences (all) | 0 / 15 (0.00%) 0 | 1 / 16 (6.25%) 1 | |
| Post procedural contusion subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 16 (0.00%) 0 | |
| Procedural headache subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 3 / 16 (18.75%) 3 | |
| Vascular disorders Hematoma subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 2 / 16 (12.50%) 2 | |
| Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 1 / 16 (6.25%) 1 | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 2 / 16 (12.50%) 2 | |
| Paraesthesia subjects affected / exposed occurrences (all) | 0 / 15 (0.00%) 0 | 1 / 16 (6.25%) 1 | |
| Gastrointestinal disorders Diarrhea subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 1 / 16 (6.25%) 1 | |
| Nausea subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 2 / 16 (12.50%) 2 | |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 15 (6.67%) 1 | 0 / 16 (0.00%) 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 | <p>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</p> <p>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</p> <p>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</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported