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

LP024

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Background

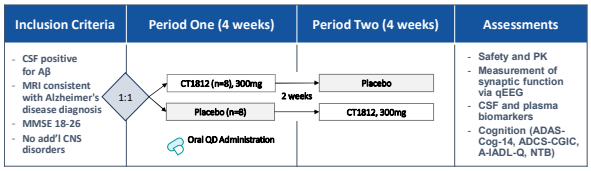
- CT1812 is an experimental, orally delivered, small molecule in development for Alzheimer's disease (AD) and dementia with Lewy bodies (DLB)
- CT1812 is a ligand for the sigma-2 receptor and evidence from *in vitro*, *in vivo* and clinical trials indicates that it can modulate the binding of toxic amyloid beta oligomers to their targets on neurons[1]
- Changes in brain activity and connectivity in AD can be reliably measured with resting state electroencphalography[2]
- **Key Objective: to determine whether four weeks of CT1812 treatment can alter synaptic activity as measured by quantitative electroencephalography (EEG)**

Primary Aims:

- 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 through quantitative EEG measurements
- Exploratory Aims:
  - Measure changes in exploratory cerebrospinal fluid (CSF) and plasma biomarkers, including synaptic damage biomarkers, measured at baseline and at the end of each treatment period
  - Evaluate changes in cognitive and global functioning, as measured by: ADAS-Cog-14, ADCS-CGIC, A-IADL-Q, NTB
  - Evaluate additional quantitative EEG measures that have shown promise such as alpha (8-13 Hz) and beta (13-30 Hz)

Methods

A pilot phase 2, single site, double-blind, placebo controlled, crossover design study (SEQUEL, COG0202) was conducted in 16 participants with mild to moderate AD (NCT04735536).



Key Inclusion and Exclusion Criteria:

- Meet CSF biomarker definition of AD[3]
- MMSE: 18 to 26, inclusive
- MRI consistent with AD and without significant abnormality
- Other exclusions: major depression, schizophrenia, bipolar disorder
- Participants on a stable regimen of AChE Inhibitors or memantine were permitted

Cognition and Biomarkers:

- Cognition was assessed before and after each treatment period
- CSF was drawn for biomarker assessment at screening and on days 29 and 72

Quantitative EEG:

Quantitative EEG was performed before and after each four-week treatment period. From eyes-closed (but vigilant) resting-state data, optimal artefact-free epochs were visually selected by experienced EEG technicians.

Change from baseline in relative spectral power for theta (4-8 Hz), alpha (8-13 Hz), and beta (13-30 Hz) frequency bands, and functional connectivity (corrected amplitude envelope correlation, AECc[4]) were ranked outcomes comparing the CT1812 to the placebo treatment periods 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.

Table1: Participant Demographics and Baseline Characteristics

	Placebo then CT1812	CT1812 then Placebo	Overall
Age - years	N=8	N=8	N=16
Mean (SD)	65.6 (6.2)	67.3 (9.7)	66.4 (7.9)
Min, Max	54, 74	51, 81	51, 81
Female sex - no. (%)	4 (50)	4 (50)	8 (50)
Race			
White	8	8	16
Other	0	0	0
Ethnicity			
Not hispanic	8	8	16
MMSE at Screening			
Mean (SD)	21.4 (1.7)	20.8 (3.0)	21.1 (2.4)
Min, Max	19, 25	18, 26	18, 26
APoE Status - no. (%)			
e3/e3	1 (12.5)	4 (50)	5 (31.3)
e3/e4	4 (50)	2 (25)	6 (37.5)
e4/e4	3 (37.5)	2 (25)	5 (31.3)
Time since Diagnosis - years			
Mean (SD)	1.4 (1.3)	0.9 (0.6)	1.1 (1.0)
Min, Max	0.3, 3.5	0.3, 1.8	0.3, 3.5

Results

- ***Safety findings*** were similar to previous studies with CT1812. There were no deaths, no serious adverse events (SAEs), no severe AEs and no discontinuations due to AEs. There was one participant with mild elevation of liver enzymes which returned to normal with study drug discontinuation. The most common AEs while on CT1812 were nausea and headache.
- ***Biomarkers:*** There were no observed changes with CT1812 in CSF measurements of Abeta 1-40, Abeta 1-42, GFAP, Nfl, total tau, pTau181, pTau217, chitinase-3-like protein 1, neurogranin, neural pentraxin, Trig rec expressed on MC2, SNAP25, vesicle-associated membrane protein 2.

Table2: Summary of Adverse Events

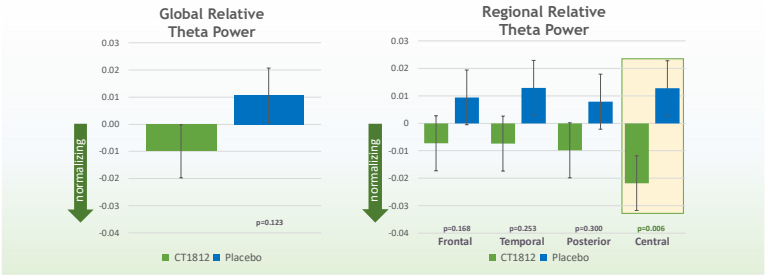
	Placebo N=15	CT1812 N=16
Number of Subjects with at least one:		
TEAE[1]	6 (40%)	11 (69%)
Mild	4 (27%)	7 (44%)
Moderate	2 (13%)	4 (25%)
Severe	0	0
TEAE related to study drug	3 (20%)	3 (19%)
TEAE graded as severe	0	0
Serious TEAE	0	0
TEAE leading to d/c[2]	0	0
TEAE leading to death	0	0

1 - Treatment emergent adverse event
2 - Discontinuation

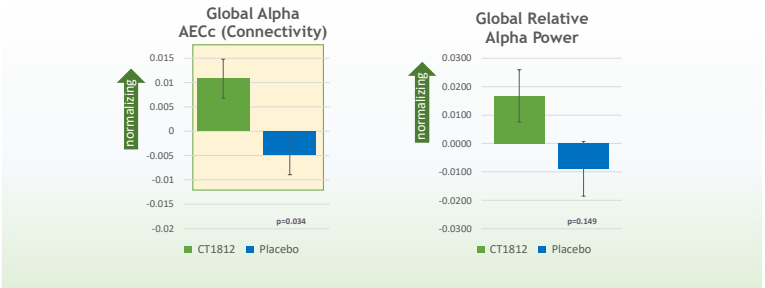
- ***Cognitive and Global Functioning***: There were no changes between placebo and CT1812 treatment periods in ADAS-COG14 (delta 0.2, 1.3 SE, p=0.89), CGIC (delta 0, 0, p = 0.75), A-IADL (delta -3.5, 1.9 SD, p=0.083), NTB sub-scores.

Quantitative EEG Data

All prespecified EEG parameters showed consistent trends of improvement in the treated group, with significant decreases in central relative theta power and increases in global alpha AECc.



Increased relative theta power, which is considered the most robust AD-related marker of oscillatory slowing, consistently normalized in all regions.



Global AECc, a marker of functional connectivity, increased in the prespecified alpha frequency band, indicating improved communication between brain regions.

Conclusions

- CT1812 was generally safe and well tolerated in this small pilot study
- CT1812 treatment showed improvement of EEG parameters that are consistent in magnitude and effect size with previously reported trials[5]
- No changes were observed in biomarkers or clinical cognitive outcomes
- Given the limited size and the duration of this study, these data are promising evidence of 1) the ability of CT1812 to enhance synaptic activity, and 2) of resting-state EEG as a sensitive short-timespan outcome measure

CT1812 is an experimental therapeutic not approved by FDA or EMA

CT1812 may offer an alternative approach to modulate amyloid oligomer toxicity and is currently in Phase 2 studies in *mild to moderate AD (NCT03507790), early AD (NCT05531656) and DLB (NCT05225415)*.

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References
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3. ***Hansson*** *et al. 2021 Alz & Dementia, 17, e054883;* ***Blennow*** *et al., 2022 Clin Chem Lab Med, 61: 234*
4. ***Hipp*** *et al., 2012 Nature Neurosci 15: 884*
5. ***Scheltens*** *et al., 2018 Alz Res Ther 10: 107;* ***Briels*** *et al., 2020 Clin Neurophys 131: 88*

Other Posters and Presentations relating to CT1812 from Cognition Therapeutics: van Dyck (8:45am Friday), Lizama (P075) et al and Di Caro (LP057) et al