SHIMMER: Baseline Data and Early Lessons from the Ongoing Phase 2 Signal-finding Study of CT1812 in Mild-to-Moderate Dementia with Lewy Bodies (DLB)

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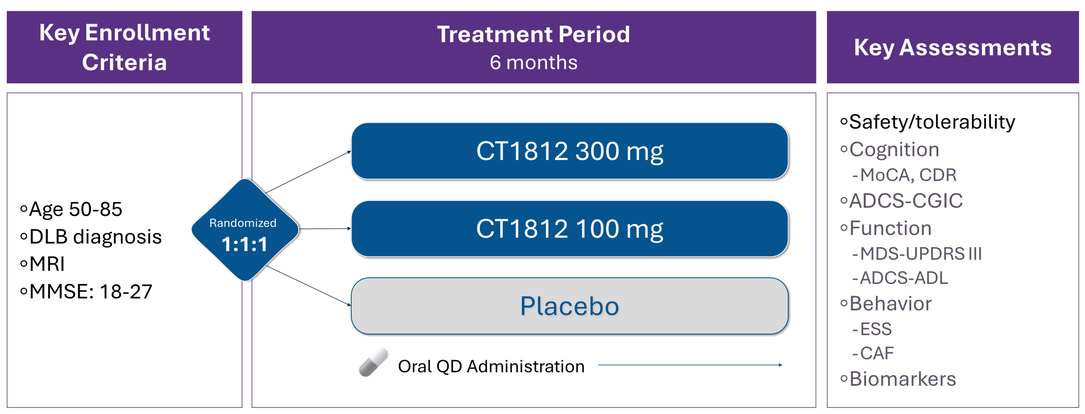
Coming soon: Readout from first signal-finding study of CT1812 in DLB

Background

- CT1812 is an experimental, oral small molecule in clinical development for dementia with Lewy bodies (DLB) and Alzheimer's disease (AD)
- CT1812 is a sigma-2 receptor modulator that displaces and prevents the binding of toxic oligomers of alpha-synuclein and amyloid beta
- DLB is considered a disease of alpha-synuclein, however a significant portion of individuals also have pathological levels of amyloid beta[1, 2]
- Baseline characteristics are reported here from the first ongoing clinical study of CT1812 in adults with mild-to-moderate DLB

Methods

- The COG1201 'SHIMMER' study is a multi-center, double-blind, placebo-controlled, parallel design clinical trial evaluating 2 doses of CT1812 versus placebo for six months
- Inclusion criteria included age 50-85 years, meeting criteria for probable DLB (as defined by the 4th report of the DLB Consortium - McKeith et al. 2017), MMSE 18-27 and excluding patients with other neurological co-morbidities
- 130 participants were randomized evenly to receive 300 mg or 100 mg CT1812, or placebo PO daily and assessed for safety, tolerability and exploratory efficacy and biomarker measures
  - First patient in: May 2022
  - Last patient randomized: May 2024



ADCS, Alzheimer's Disease Cooperative Study; ADL, activities of daily living; CAF, clinical assessment of fluctuations; CGIC, clinical global impression of change; ESS, Epworth sleepiness scale; MMSE, mini-mental state examination; MRI, magnetic resonance imaging; QD, daily; MoCA, Montreal cognitive assessment; CDR, cognitive drug research battery; MDS-UPDRS, Movement Disorder Society unified Parkinson's disease rating scale;

Outcomes

Safety:

Evaluation of adverse events, physical and neurological exams, vital signs, ECG, clinical laboratory tests, change in usage of concomitant medications and Columbia-Suicide Severity Rating Scale (C-SSRS)

Exploratory Efficacy:

Change from baseline at Day 28, 98 and 182 for the following exploratory outcomes will be assessed for the combined CT1812 (100 mg and 300 mg) treatment groups vs. placebo:

Scale	Range	Higher score indicates:
MoCA	0-30	Less cognitive impairment
ADCS-CGIC	Up to 7	Worsening compared to baseline
CAF	0-16	More severe fluctuations
ESS	0-24	Excessive daytime sleepiness (≥10 = abnormal)
MDS-UPDRS III	0-136	More severe motor symptoms
ADCS-ADL	0-78	Less functional impairment

Pre-planned subgroups by baseline α-syn, amyloid positivity and p-Tau 217 will be evaluated

Biomarkers:

Alpha-synuclein (α-syn) will be assessed via skin biopsies at baseline and end of study. Amyloid status at screening is determined by APS2 score. The APS2 score takes into account plasma p-Tau217/Tau217 and Aβ42/40 ratio to predict the presence of brain amyloid >25 centiloids via PET. Change from baseline levels of plasma biomarkers including GFAP, p-Tau 217 and NfL will be assessed.

Biology	Biomarker	Method	Matrix
DLB status & progression	α-syn	Syn-One Test*	Skin Biopsy
	Total α-syn	Immunomagnetic reduction (IMR)	Plasma
	Phospho-α-syn	IMR	Plasma
	DOPA decarboxylase	Simoa	Plasma
Core Biomarker	Amyloid status	PrecivityAD2™†	Plasma
	Aβ42, Aβ40, ratio	Simoa	Plasma
	pTau217	Simoa	Plasma
	pTau181	Simoa	Plasma
Neuroinflammation	GFAP	Simoa	Plasma
Neurodegeneration	NfL	Simoa	Plasma

*CND Life Sciences
†C2N Diagnostics

Adjustments to the protocol:

- CSF collection was initially required but was made optional through a protocol amendment to enhance recruitment and was collected from a limited number of subjects.
- In the post-COVID-19 setting, a protocol amendment allowed for drug interruption while participants were treated with nirmatrelvir / ritonavir (Paxlovid) due to the CYP3A4 inhibition.

Baseline Characteristics

Baseline Characteristics (N=130)	
Mean Age (SD)	72.8 years (6.70)
Gender: Male	81.5%
Race: White	91.5%
Non-Hispanic or Latino	96.9%
MMSE (SD)	24.0 (2.66)

Baseline Efficacy Parameters (N=130) Mean (SD)	
MoCA	18.4 (4.94)
CAF	5.9 (3.02)
ESS	8.4 (4.62)
MDS-UPDRS III	27.7 (13.36)
ADCS-ADL	62.5 (10.91)

Conclusions

- Baseline demographics are similar to other signal-finding studies, with a slightly higher percentage of male participants
- When compared to the DIAMOND-Lewy study[3], a UK study that included 72 subjects with DLB, SHIMMER participants have slightly higher average baseline scores on MMSE and MoCA and lower score on MDS-UPDRS III
- Study data are anticipated by year-end 2024

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Acknowledgements

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CT1812 is an investigational therapeutic that has not been approved for any use by the US Food and Drug Administration or other health authority

References:
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