Proposed Study Design of Zervimesine for Treatment of Psychosis in Dementia with Lewy Bodies

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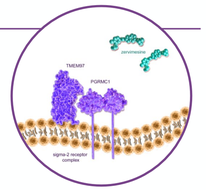
Background



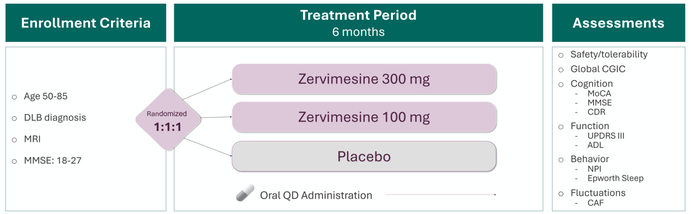
Zervimesine (CT1812)* is an oral, once-daily small molecule ligand of the sigma-2 receptor complex on neurons, that blocks binding of pathogenic α-synuclein and Aβ oligomers to synaptic receptors. Approximately 650 people with Alzheimer's disease, dementia with Lewy bodies (DLB), and dry age-related macular degeneration have received zervimesine in clinical trials. Zervimesine has been generally well tolerated in clinical trials to date.

DLB is a progressive, fatal neurodegenerative disease characterized by fluctuating neuropsychiatric, cognitive and motor symptoms. Hallucinations and delusions (psychosis) are among the most common neuropsychiatric presentations of DLB. They are also often cited as the most challenging for patients and their care partners to manage.[1]

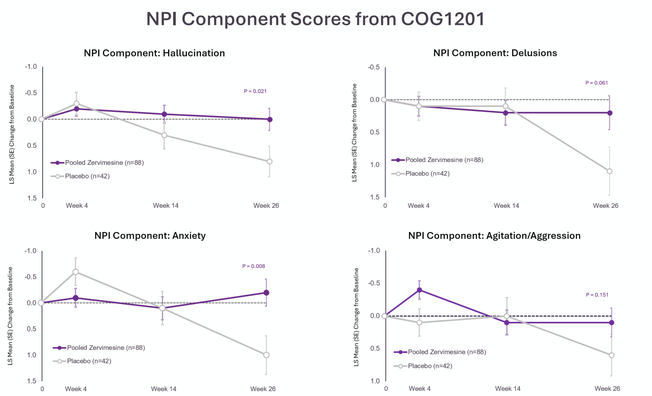
Up to 80% of DLB patients experience psychosis.[2] The off-label use of traditional antipsychotic medication is complicated due to the risk of neuroleptic sensitivity in DLB and Parkinson's disease patients, that can result in severe parkinsonism, sedation, or sudden death. Zervimesine is not an anti-psychotic agent but is a disease-modifying drug that may impact the full range of DLB symptoms. The phase 2 SHIMMER study demonstrated the potential of zervimesine to slow progression of core DLB symptoms, notably hallucinations and delusions[3]. The key objective of the zervimesine development program is to demonstrate that zervimesine treatment can stabilize psychosis in people living with DLB.

Rationale

Cognition completed COG1201 'SHIMMER', a double-blind, placebo controlled, randomized Phase 2 trial (NCT05225415) of zervimesine in 130 adults with mild-to-moderate DLB.



COG1201 met its primary endpoint of safety and tolerability. In addition, there were consistent trends of slowing progression in measures of behavior, cognition, function and movement in zervimesine-treated participants versus placebo[3]. Notably, the study demonstrated a clear effect on the 12-item neuropsychiatric inventory (NPI), with strongest impact on hallucinations, delusions, anxiety and aggression/agitation components.



Support for NPI (H+D)

Typical and atypical antipsychotics have rapid onsets of action but no impact on underlying disease. Data from the signal-finding COG1201 study in DLB demonstrated a slowing of progression with zervimesine treatment across the range of DLB symptomatology. Placebo-treated participants continued to worsen overall during the study. The strength of the stabilization of neuropsychiatric symptoms indicate that psychosis could be a marker of zervimesine's disease-modifying effect.

Definitive clinical studies require the assessment of a primary endpoint that is measurable by validated and accepted clinical instruments. No such tool yet exists to measure the totality of the symptoms experienced by individuals with the heterogeneous and multi-symptomatic features of DLB. The NPI measures components of psychosis (hallucinations and delusions) and other behavioral symptoms. Cognition proposes the hallucinations and delusions components of the NPI or NPI-C as the primary endpoint of the planned Phase 3 study.*

Both the NPI and NPI-C incorporate responses from an informed caregiver who rates the frequency and severity of neuropsychiatric behaviors from the previous month. Because these tools assess changes over a month, they are unaffected by the day-to-day symptom fluctuations characteristic of DLB.

The proposed Phase 3 study will recruit individuals with DLB who have psychosis symptoms at baseline. Data from SHIMMER re-analyzed with these criteria are plotted in Figure 2.

FIGURE 2a

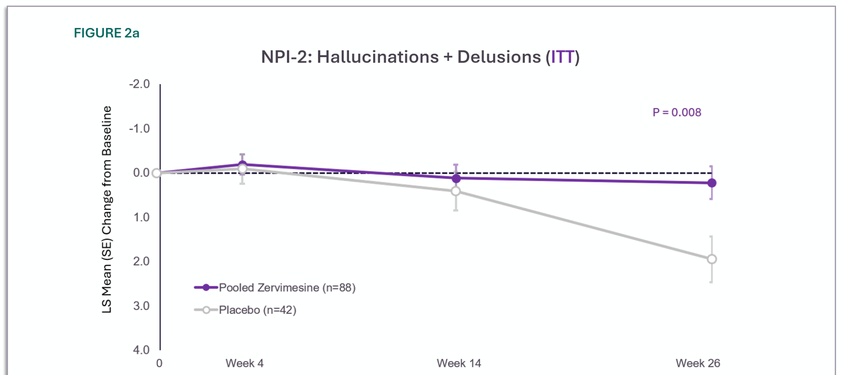
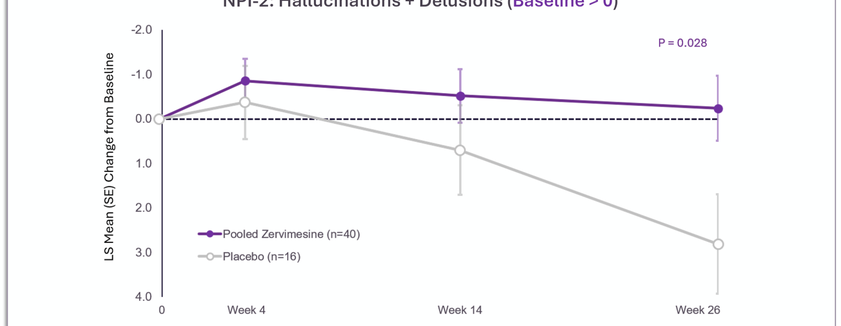


FIGURE 2b



** Zervimesine is an investigational candidate, and as such has not been reviewed or approved by regulatory authorities in any jurisdiction. The contents of this poster describe the planned Phase 3 study design, which remains subject to regulatory review and clearance.*

Zervimesine has the potential to be the first treatment that slows the progression of psychosis in DLB.

The proposed Phase 3 study will assess the impact of zervimesine treatment on hallucinations and delusions in people with DLB psychosis.

Conclusions

Following meetings with the FDA Divisions of Neurology and Psychiatry, Cognition Therapeutics is planning to conduct a randomized (1:1), double-blind, multicenter, placebo-controlled study assessing the ability of zervimesine to attenuate the progression of psychosis symptoms in individuals with DLB. Following screening, participants will be treated with either 100 mg of once-daily oral zervimesine or placebo for nine months. Individuals on a stable regimen of off-label antipsychotics will be eligible; use of anti-psychotic rescue medication for those who progress in their symptoms will also be allowed.

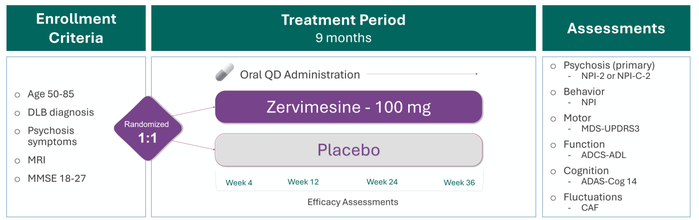
Key Inclusion Criteria

DLB Dx	Diagnosis of probable DLB (McKeith 2017 criteria)
Psychosis	History of one or more episodes of hallucinations and/or delusions in the 4-weeks prior to screening

Proposed Primary

NPI or NPI-C	(hallucinations + delusions) • Change from baseline to Month 9

Proposed Phase 3 Schematic



Acknowledgements

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ABBREVIATIONS: **ADAS-Cog 14**: Alzheimer's Disease Assessment Scale-Cognitive Subscale-14 item version; **ADCS-ADL**: Alzheimer's Disease Cooperative Study-Activities of Daily Living; **CAF**: Clinicians Assessment of Fluctuations; **MDS-UPDRS3**: Movement Disorder Society-Unified Parkinson's Disease Rating Scale Part III; **MMSE**: Mini Mental State Exam; **NPI**: Neuropsychiatric Inventory; **NPI-2**: NPI Hallucinations and Delusions subdomains; **NPI-C**: NPI-Clinician

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