A GLOBAL STATISTICAL TEST APPROACH TO CLINICAL TRIALS WITH ZERVIMESINE FOR DEMENTIA WITH LEWY BODIES

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COGNITION™ Therapeutics

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Aims:

- Zervimesine (CT1812) is an experimental, oral, brain-penetrant, small molecule therapeutic in development for age-related neurodegenerative diseases, including dementia with Lewy bodies (DLB).
- DLB manifests with diverse symptomatology.
- Zervimesine treatment addresses the underlying DLB pathophysiology thereby impacting multiple symptoms including neuropsychiatric, motor, cognitive, and fluctuations in attention.
- As there is no accepted global outcome measure designed specifically for DLB, a global statistical test (GST) approach could be useful to capture the multi-dimensional symptomatology of DLB.

Why a composite?

- The diagnosis of DLB requires evidence of dementia and the presence of two or more core features (e.g. cognitive fluctuations, visual hallucinations, and parkinsonism).
- A composite endpoint comprised of multiple domain-specific measures would allow trial sponsors to enroll and assess treatment effects on a broad spectrum of DLB patients with diverse symptomatology.

Background:

Zervimesine was studied in COG1201, a double-blind, placebo-controlled Phase 2 trial in 130 adults with mild-to-moderate DLB (NCT05225415; SHIMMER).[1]

Methods:

Data from the COG1201 trial as well as published findings from patient, caregiver, and physician surveys were employed to create a composite endpoint that we propose for future DLB studies.

The composite endpoint includes:

- 4-item Neuropsychiatric Inventory (hallucinations, delusions, anxiety, agitation/aggression)
- Cognitive Drug Research Battery – Quality of Memory
- Movement Disorder Society – Unified Disease Rating Scale III, and
- Clinician Assessment of Fluctuation

The ADCS-ADL could be included within the overall GST composite or as an independent measure of clinical meaningfulness.

Figure 1 **GST Components Assess Different DLB Symptomatology[2]**

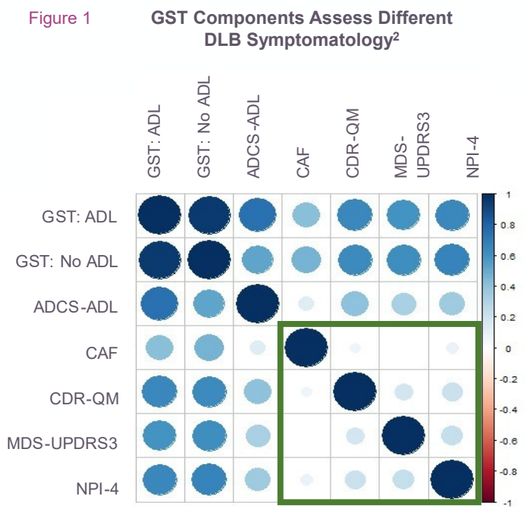


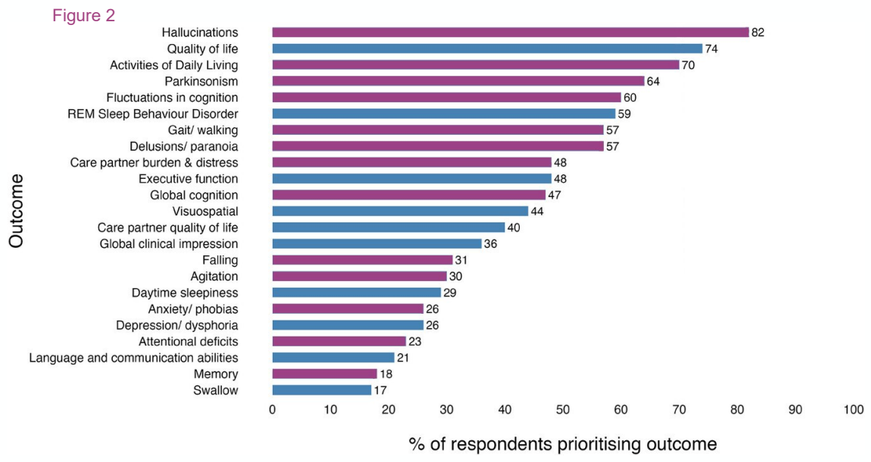
Figure 1 shows limited correlation (lighter and smaller dots indicate less correlation) of proposed endpoints included in the global composite endpoint.

- The composite combines different component clinical endpoints
- The component clinical endpoints move relatively independently
- Standardized Z scores for each component endpoint are averaged so each is weighted equally in the overall score

DLB currently has no validated fit-for-purpose global outcome measure.

A GST approach may allow measurement of treatment effects that captures the multi-dimensional symptomatology of DLB.

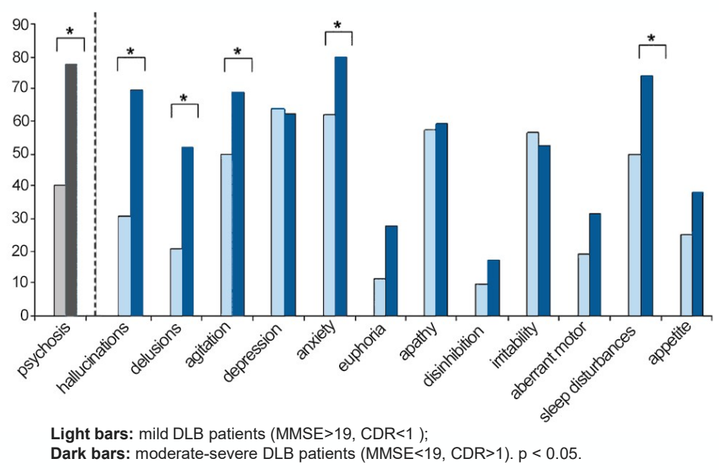
Figure 2



Kane et al (2025) published findings from a survey of clinicians, DLB patients, and their care partners who ranked symptoms by degree of importance (Figure 2 above).[3] Purple bars denote the outcomes incorporated in the proposed GST.

Borroni et al (2008) identified the percentage of DLB patients with mild (light bars) and moderate (dark bars) disease who manifest various neuropsychiatric symptoms (Figure 3 below).[4] From this, we can identify symptoms that significantly worsen as DLB progresses.

Figure 3



Light bars: mild DLB patients (MMSE>19, CDR<1);
Dark bars: moderate-severe DLB patients (MMSE<19, CDR>1). p < 0.05.

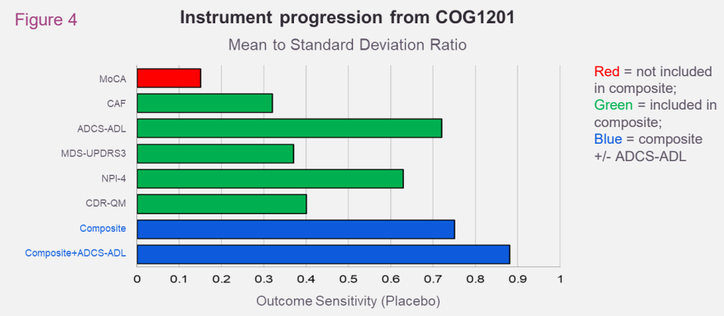
Note that hallucinations, delusions, agitation, and anxiety are captured in the NPI-4, which is included in the proposed composite measure. These symptoms progress as patients worsen and are also highly ranked in Figure 2 as important.

Besides neuropsychiatric symptoms, other symptoms ranked as important to patients are included in the proposed composite endpoint including parkinsonism, cognition, and cognitive fluctuations.

Results:

The composite shows a greater signal to noise (mean to SD ratio) than its individual components indicating greater efficiency as a clinical trial endpoint (Figure 4).[2]

Figure 4 **Instrument progression from COG1201**



Utilizing the COG1201 dataset, we found that baseline and change from baseline composite scores correlated significantly with ADCS-ADL (r=0.53, 0.52, respectively, p<0.0001) indicating clinical meaningfulness of the non-ADL components.[2]

Figure 5 **ADCS-ADL Favors Treatment with Zervimesine**

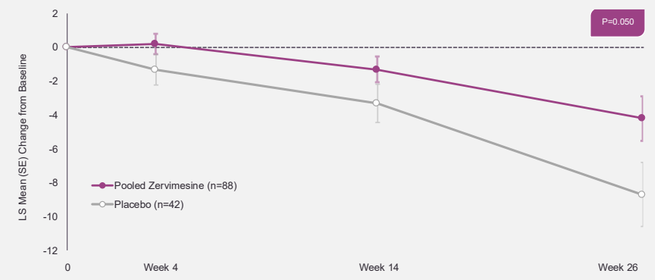
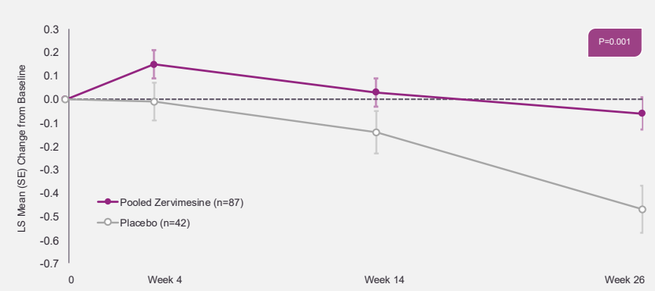


Figure 6 **Composite Endpoint Favors Treatment with Zervimesine**



Zervimesine treatment resulted in 52% slowing of progression of ADCS-ADL relative to placebo (p=0.0503) (Figure 5).

Post-hoc analysis using the composite endpoint demonstrates an 87% slowing of progression with zervimesine treatment (p=0.0008) (Figure 6).

Based on the COG1201 study data, zervimesine could achieve 90% power to detect a significant difference from placebo on this composite with fewer than 250 study participants.

Conclusions:

- Endpoints ideally measure changes in domains that
  a) are important to patients, and
  b) progress with disease so that changes can be detected.
- The proposed GST composite approach allows assessment of a general treatment effect in DLB without specifying a single-symptom primary outcome.
- This approach may effectively measure the variety of symptoms that DLB patients display.
- While treatment effects for specific symptoms can be measured through validated assessments, composite approaches are important for physicians and regulators to understand the full impact of a drug in this diverse and variable disease.

Disclosures:

MG is a paid consultant and shareholder in Cognition Therapeutics; SH, SD, CD are employees of Pentara Corporation, which consults for more than 30 companies in the Alzheimer's disease space including Cognition Therapeutics; SK provided biostatistics support; JH is a consultant for more than 15 companies in the neuroscience space; AC and JI are Cognition Therapeutics employees

References:

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3. Kane et al. 2025 Alzheimer's Dementia 11:e70134
4. Modified from Borroni et al. Arch Gerontol Geriatr. 2008 46:101-6