Alzheimer's Disease Pivotal Trial Design for Zervimesine (CT1812) Following an End-of-Phase 2 Meeting with FDA

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Efficacy Signals in Phase 2 Support Advancing Zervimesine into Registrational Studies

Background

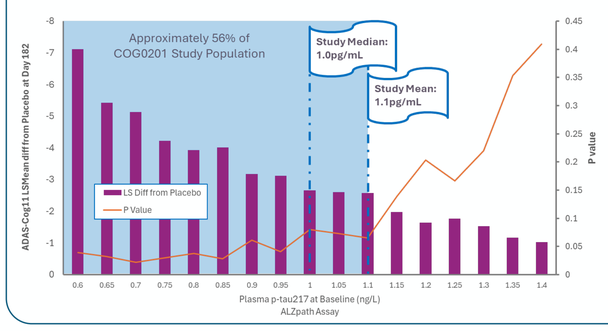
- Zervimesine (CT1812) is an oral, small molecule, therapeutic in development for Alzheimer's disease (AD) and dementia with Lewy bodies (DLB)
- Zervimesine is a sigma-2 receptor modulator that reduces the affinity of amyloid oligomers for their synaptic receptors on neurons
- Phase 2 data from the COG0201 'SHINE' exploratory efficacy study (NCT03507790) in 153 adults with mild-to-moderate AD showed promising trends, which were most robust in individuals with lower baseline p-tau217
- Registrational strategy was discussed with FDA during an end-of-Phase 2 meeting
- Zervimesine has not been approved for any use by the US Food and Drug Administration or other health authority

Proposed Study Population

- Age 50 – 85, community based
- Dx by Jack *et al,* 2024[1] criteria with 6-month decline
- MMSE 18-26
- Confirmed amyloid via PET, CSF or approved plasma-based diagnostic
- Baseline plasma p-tau217 below ~1.0 pg/mL (Alzpath)*
- Stable regimen of AChE inhibitors or memantine
- No prior exposure to anti-amyloid antibodies

Rationale for p-Tau217 Enrichment

COG0201 Results:
ADAS-Cog11 Change from Placebo and P-value

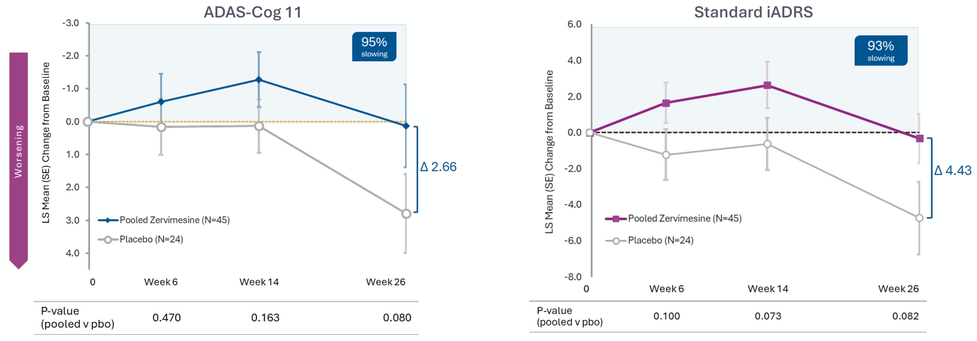


** Individuals with lower AD pathology at baseline, as reflected by lower levels of p-tau217, have a greater response to amyloid-lowering therapies. This has been observed in published peer results [2, 3, 4] and in the Phase 2 COG0201 SHINE clinical trial (left).*

Treatment Period

FDA concurred that six-month studies would be adequate for registration based on efficacy signals in 26-Week COG0201 study (below)

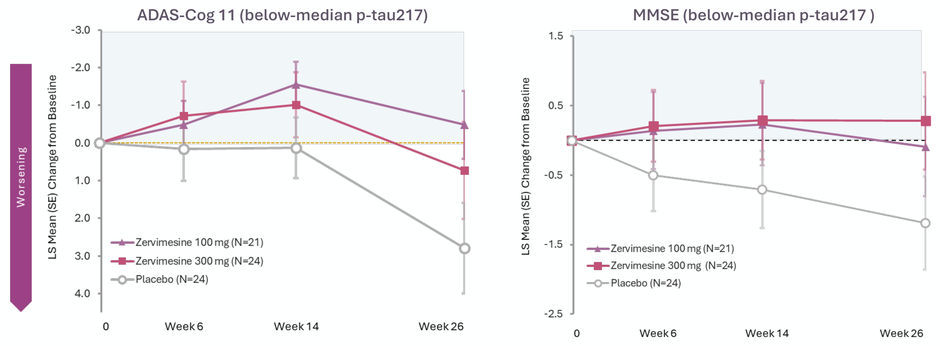
Efficacy Measures in Below-median p-Tau Population



Dose Selection

- 100 mg zervimesine selected for registrational studies:
  - Similar cognitive and functional effects observed with 100 and 300 mg
  - Fewer discontinuations due to AEs: 0 for 100 mg, 21.6% for 300 mg
  - Fewer laboratory abnormalities (AST / ALN >3X ULN): 0 with 100 mg, 10 with 300 mg

Efficacy Measures in 100mg and 300mg Arms



Registrational Plan:

Population:	Adults with mild-to-moderate Alzheimer's disease - Confirmed amyloid by PET, CSF assay or approved blood test - Plasma p-Tau217 below ~1.0 pg/mL
Tx period:	6 months
Dose:	100 mg zervimesine vs placebo; randomized 1:1
Endpoints:	Composite cognitive and functional measure
Scheme:	Two Phase 3 studies followed by an open-label extension

Endpoints and Powering

- FDA concurred that either iARDS or co-primary endpoints would be appropriate as considered:
  - iADRS with independent look at components and secondary outcomes
  - Traditional co-primary outcomes measuring ADAS-Cog with ADCS-ADL / ADCS-CGIC

Endpoint	Assumed Mean Treatment Difference[1]	Pooled SD	(N) Completers/ Treatment Group Needed for 90% Power	Power with 277 Completers/Treatment Group
iADRS	3.9	8.506	101	>95%
ADAS-Cog13	2.6	5.85	108	>95%
ADCS-ADL	1.9	6.88	277	90%
ADCS-CGIC	0.376	1.101	182	>95%
MMSE	1.2	2.974	131	>95%

[1] Assumed mean treatment differences are 20% smaller than what were observed in the SHINE study.

Conclusions:

- Following an end-of-Phase 2 meeting, Cognition and FDA agreed upon the basic study elements for zervimesine registrational trials in Alzheimer's disease, notably:
  - 6-months would be a sufficient treatment period
  - Participants with lower plasma p-Tau217 levels would be enrolled to enrich for patients most likely to benefit from zervimesine treatment
- The proposed schema, including treatment period, enrollment target, and endpoints are being carefully considering and may not be initiated exactly as described here

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Acknowledgements

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References:
1. Jack CR Jr, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alzheimers Dement. 2024;20(8):5143-5169. doi:10.1002/alz.13859
2. Mintun, et al. Predicting Efficacy in Donanemab-Treated Participants. Slides presented at Clinical Trials on Alzheimer's Disease 2023
3. Sims et al., 2023 Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA
3. Eisai Presents new LEQEMBI® (LECANEMAB-IRMB) Investigational subcutaneous formulation interim study results and clinical improvement data in earlier stages of early Alzheimer's disease from additional analyses of CLARITY AD at the Clinical Trials on Alzheimer's Disease (CTAD) conference [Press release Oct. 26, 2023]

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