Rapid and Durable Improvements in Cognitive and Neurophysiological Outcomes in mild-to-moderate AD patients treated with the synaptic regenerative drug, Tazbentetol

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BACKGROUND

Glutamatergic synapse loss is a core feature of Alzheimer's pathogenesis *

- starts early, before symptoms
- correlates with cognitive decline
- point of convergence among diverse pathogenic processes
- having more synapses is associated with cognitive resilience in the face of AD pathology
- **Tazbentetol (SPG302) is being developed as the first synaptic regenerative therapy for Alzheimer's**

TAZBENTETOL

- novel, first-in-class
- rapid-acting
- synaptic regenerative
- small molecule administered as an oral tablet
- regenerative – promotes the formation of new dendritic spine synapses

Illustration of tazbentetol effects on dendritic spine density *in vivo* (CA1 apical dendrites)

Tazbentetol found to restore synaptic density within 2-4 weeks of daily treatment in preclinical models[10,11] and in 3 species (mouse, rat, dog)

PHASE 2a TRIAL DESIGN

Part 1 (Double Blind Placebo Controlled) 4 weeks → Part 2 (Open Label Extension) 24 weeks* → Compassionate Use (SAS) 2 years

Mild-to-Moderate AD SMMSE score of 16-26 (inclusive)

- 300mg (N=12, 8 active : 4 placebo)
- 150mg (N=12, 8 active : 4 placebo)

Key Endpoints	
Functional	• Standardized Mini-Mental State Examination • Clinical Dementia Rating Sum of Boxes • Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory
Biomarker	• Quantitative EEG: Resting state and auditory-evoked P300

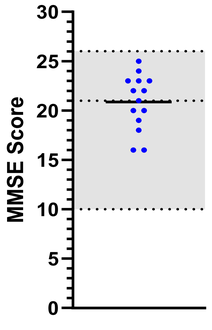
* OLE period extended beyond readout at 24 weeks to 40 weeks LTFU

Demographics

Age	
n	24
Mean	71.5
SD	8.1
Median	73.5
Minimum	51
Maximum	82
Sex	
Female	50%
Male	50%

Race	
American Indian / Alaska Native	0%
Asian	0%
Black or African American	0%
Native Hawaiian or Other Pacific Islander	0%
White	92%
Not Reported	0%
Other	8%
Unknown	0%
Ethnicity	
Hispanic or Latino	0%
Not Hispanic or Latino	100%
Not Reported	0%
Unknown	0%

Baseline Characteristics



SMMSE ranges:

- Normal cognitive function: 27-30
- Mild Cognitive Impairment: 21-26
- Moderate Cognitive Impairment: 10-20
- Severe Cognitive Impairment: <10

Participant recruitment balanced between mild and moderate AD stages as defined by SMMSE

p-TAU-217 ranges

- Negative: ≤ 0.33 pg/mL
- Intermediate: > 0.33 - < 0.56 pg/mL
- Positive: ≥ 0.56 pg/mL

Participants had a positive pTau217 result at baseline

50% of participants were on a stable dose of donepezil prior to trial entry, which was maintained throughout the trial

Results

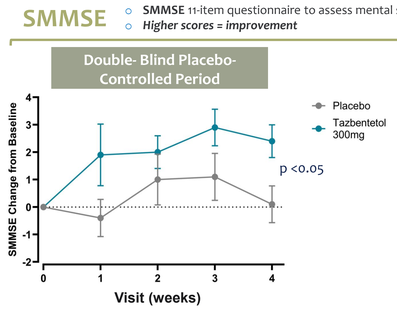
Safety & Tolerability

- Safety & Tolerability in AD participants mirrors the excellent profile observed in healthy adults in Phase 1, Phase 2 ALS and SCZ cohorts, and an intermediate sized expanded access protocol (ISEAP) in ALS (>35,000 doses)
- No clinically significant shifts or safety signals in hematology, chemistry, vital signs
- Most common treatment-emergent adverse events (TEAEs): Infections 30.4% at 24 weeks .TEAEs were unrelated to the study drug. One serious adverse event: femoral neck fracture

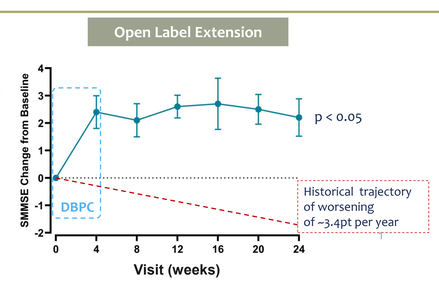
Efficacy – SMMSE and CDR-SB (all participants)

SMMSE

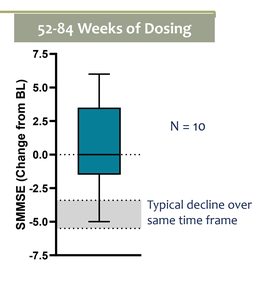
- **SMMSE** 11-item questionnaire to assess mental status
- ***Higher scores = improvement***



8 pooled placebo and 8 on 300 mg

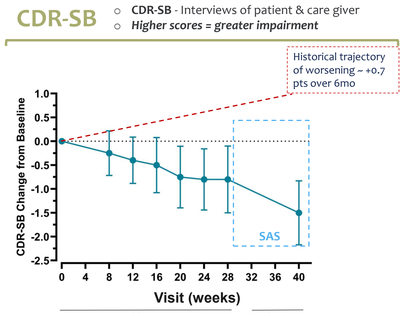


8 at 300 mg 0-4 wks then all 12 in cohort 300mg after 4 wks



CDR-SB

- **CDR-SB** - Interviews of patient & care giver
- ***Higher scores = greater impairment***



❖ **Rapid, significant improvement during DBPC period**

Pharmacodynamic marker – EEG (all participants)

Treatment goal: reduce low/high frequency ratios, restoring faster, more efficient brain function

EEG is a neurophysiological outcome measure

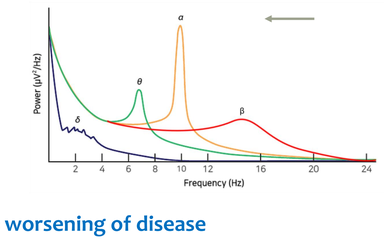
- Mainly reflects synchronized excitatory synaptic currents
- Objective, quantitative, non-invasive, patient-friendly
- **Sensitive to changes in synaptic function / density ***

EEG changes are well established in AD

- Signature changes in spectral power and connectivity **
- **Significant slowing of cortical rhythms, including:**
  - Increase in "Slow" **theta (θ)** and **delta (δ)** frequencies
  - Decrease in "Fast" **alpha (α)** and **beta (β)** frequencies
- **Correlates with cognitive decline and pathology ****

Two ratios used to measure slowing of activity

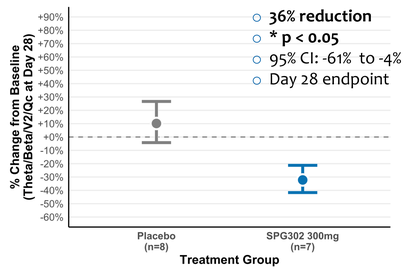
- **Theta / Beta** ratio
- **Global Slowing Index:** $(\delta + \theta) / (\alpha + \beta)$



Increases in these ratios = worsening of disease

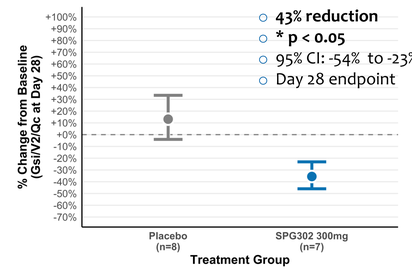
EEG biomarker evidence supporting rapid benefit during the placebo-controlled treatment period

Reduced Theta / Beta



- **36% reduction**
- ***** p < 0.05**
- 95% CI: -61% to -4%
- Day 28 endpoint

Reduced Global Slowing Index (GSI)



- **43% reduction**
- ***** p < 0.05**
- 95% CI: -54% to -23%
- Day 28 endpoint

Clinical Significance

- Theta-beta ratio is known biomarker in AD
- Reduction of ratio reflects improved cortical function

Clinical Significance

- GSI is a composite ratio of slow (δ + θ) to fast (α + β) activity which captures overall cortical slowing burden
- Reduction of ratio reflects improved cortical function

Tazbentetol favorable profile vs approved therapeutics

	24 Weeks of Treatment (change from baseline)						
	Lecanemab (Clarity AD Ph3)		Donanemab (Trailblazer-Alz 2 Ph3)		Tazbentetol (Ph2)	Donepezil (10mg)	
Outcome	Drug	Placebo	Drug	Placebo	Overall	Drug	Placebo
MMSE lower=impairment	-1.0	-1.3	-0.8	-1.0	**+2.0**	~ +1.3	-0.61
CDR-SB higher=impairment	~ +0.45	~ +0.65	~ +0.3	~ +0.71	**-0.81**	~ -0.06	~ +0.5

Acknowledgements

We want to give special thanks to the patients, their caregivers and family for participating in the trial. We would like to thank the site staff and teams for all the efforts for this trial.

CASE STUDY

Initial presentation

- 72-year-old woman
- Baseline SMMSE = 23, mild AD with slow decline
- Subject lived at home with husband
- Short-term memory loss, anomia, topographical disorientation, emotional lability, impaired social / etiquette skills very impaired
- Independent for personal and domestic activities of daily living (ADLs)
- Started on 300mg tazbentetol in Sept. 2024

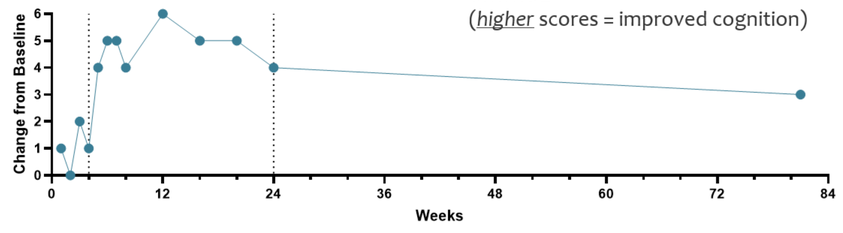
Spousal perceived benefit of treatment

- Within 3 months, husband reported:
  - ❖ able to read a book again (halfway into 2nd book at time of report)
  - ❖ watching movies again
  - ❖ able to recall story and plot lines

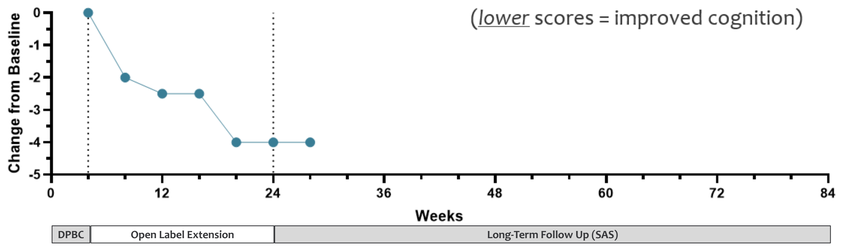
Clinical outcomes supporting perceived benefit

- Rapid, large increase in SMMSE scores during double-blind, placebo-controlled period that increased during open label extension and persisted into the SAS period (last measurement at 81 weeks)
- Rapid and large decreases in CDR-SB scores during out to last measurement made at 28 weeks

SMMSE
(*higher* scores = improved cognition)



CDR-SB
(*lower* scores = improved cognition)



CONCLUSIONS for TAZBENTETOL in AD:

- Favorable safety and tolerability
- Evidence of rapid and significant benefit in SMMSE vs placebo
- Degree and duration (>1yr) of improvement in SMMSE compare favorably to standard of care (*e.g.* donepezil affords ~1pt increase in SMMSE over baseline that begins to wane at 6months)
- Evidence of rapid benefit in the FDA-approvable outcome measure CDR-SB
- Evidence of long-term benefit in CDR-SB that increases over time
- EEG neurophysiological biomarker supports normalization of cortical activity, synaptic regeneration and 300mg once daily as active dose
- **Results support the hypothesis that synaptic regeneration may be efficacious in restoring cognitive function in AD**