Early positive signals of cognitive outcomes in mild to moderate Alzheimer patients treated with the synaptic regenerative small molecule, SPG302

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Background

Spinogenix has developed a novel small molecule synaptic regenerative therapy, SPG302, to restore synapses in AD (and other synaptopathies), with the goal of helping patients recover lost function.

This poster presents findings from a Phase 2a trial of SPG302 in AD participants (NCT06427668).

Glutamatergic synapse loss is a major proximal cause of cognitive decline in Alzheimer's disease (AD) that essentially uncouples cortical-limbic circuits involved in learning, memory and cognition[1-6]. Most glutamatergic synapses lost in AD have dendritic spines as the postsynaptic element. Studies of spine F-actin regulatory proteins link the loss of axospinous synapses in particular to cognitive decline. Accordingly, retention of dendritic spine synapses is associated with cognitive resilience in the context of AD molecular pathology and in normal aging[7-9]. Preclinical studies in an AD mouse model support the hypothesis that synaptic regeneration with SPG302 may be efficacious in AD[10].

Results from an initial cohort of mild-to-moderate AD participants treated with 300mg oral SPG302 q.d. (NCT06427668) are presented.

SPG302

SPG302 is

- 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 SPG302 effects on dendritic spine density *in vivo* (CA1 apical dendrites)

SPG302 found to restore synaptic density within 2-4 weeks of daily treatment in preclinical models[10,11] and in 3 species (mouse, rat, dog)

Preclinical POC in AD

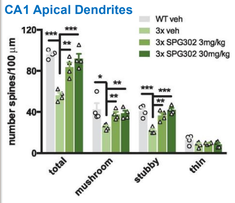
Daily treatment for 4 weeks sufficient to rescue synaptic density and memory deficits (NIH funded 1R43AG058278)

Trujillo-Estrada *et al*, 2021 – 3xTg AD mouse model

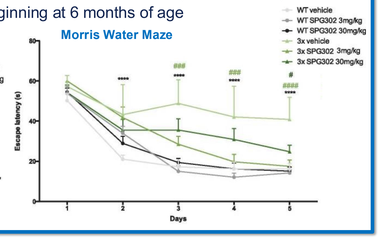
SPG302 Reverses Synaptic and Cognitive Deficits Without Altering Amyloid or Tau Pathology in a Transgenic Model of Alzheimer's Disease (PMC8804111)

- Daily treatment, 4 weeks, beginning at 6 months of age

CA1 Apical Dendrites



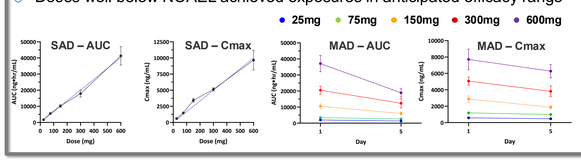
Morris Water Maze



Phase 1 Summary

SPG302 was safe & well tolerated through 600mg in healthy volunteers

- Single (SAD) and multiple (MAD) ascending oral doses from 25 to 600mg
- No SAEs; 8 TRAEs (6 Grade 1, 2 Grade 2)
- Dose proportional exposure, negligible food effect
- T1/2 1-2hrs, no accumulation across days
- Doses well below NOAEL achieved exposures in anticipated efficacy range

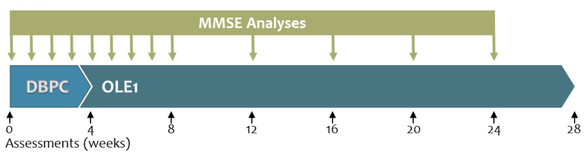


Phase 2a Trial of SPG302 in AD

DESIGN

Double blinded, Randomized (2:1), Placebo-controlled (4 weeks) period followed by an open label extension of 24 weeks in adults with Mild-to Moderate AD

4-week open label duration prompted by rapid activity of SPG302 in preclinical models



ENDPOINTS Presented

- **Safety / PK**
- **Efficacy (as changes in):**
  - **Standardized Mini-Mental State Examination (SMMSE)**
  - **Clinical Dementia Rating Sum of Boxes (CDR-SB)**

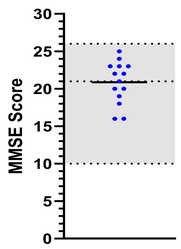
Results

Demographics (300mg cohort)

AGE	
n	13
Mean	71.6
SD	8.9
Median	73.5
Minimum	51
Maximum	81
Sex	
Female	62%
Male	38%
Woman of Childbearing Age	
Yes	0%
No	100%

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 SMMSE Scores



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

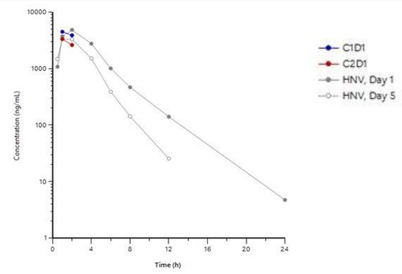
Participant recruitment balanced between mild and moderate AD stages as defined by SMMSE

SPG302 and Other Treatments

Drug	# of Patients
Donepezil	2
Denosumab	2
Memantine	1

SPG302 in combination with standard of care therapeutics was well tolerated

SPG302 PK in AD Participants



PK in AD patients appears to be comparable to that observed in healthy adults.

Safety & Tolerability

Grade	ALL Adverse Event Terms (not related)
1	Numbness on Right Index Finger
1	Increased Fatigue & Tiredness
1	Exacerbation of Hypertension
1	Patient appeared to be slightly off, depressed and slightly elevated
1	Depression family stress as precipitant
1	Cough & Malaise
1	Bloody Stool (pt has history of haemorhoids)
1	Urinary Tract infection
2	Benign Paroxysmal Positional Vertigo
2	Tooth Extraction
2	Tooth/ Gum infection

- **SPG302 was generally safe and well tolerated in AD participants**
- **There were no severe (SAEs) or treatment-related adverse events (TRAEs)**
- **4/13 patients experienced an AE unrelated to SPG302**
- **Most were Grade 1 and resolved**

Safety & Tolerability in AD participants mirrors the excellent profile observed in healthy adults in Phase 1. Combined with its ease of administration as a once-a-day oral tablet, this profile suggests SPG302 may have distinct advantages in terms of safety and compliance relative to existing SOC treatments, including monoclonal antibodies targeting amyloid beta.

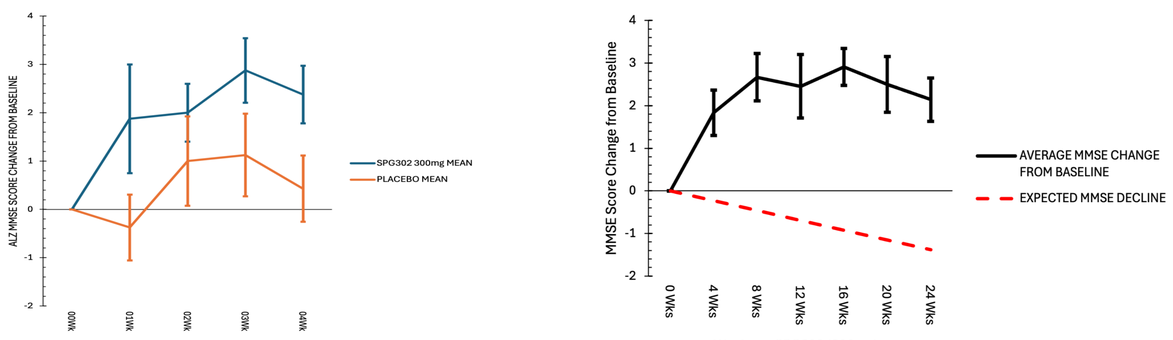
SPG302 Favorable profile vs approved therapeutics

	24 weeks of treatment						
	Lecanemab (Clarity AD Ph3)		Donanemab (Trailblazer-Alz 2		SPG302 (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

Efficacy – SMMSE

SMMSE 4-week placebo-controlled period

SMMSE 24-week open label period (weeks on treatment)

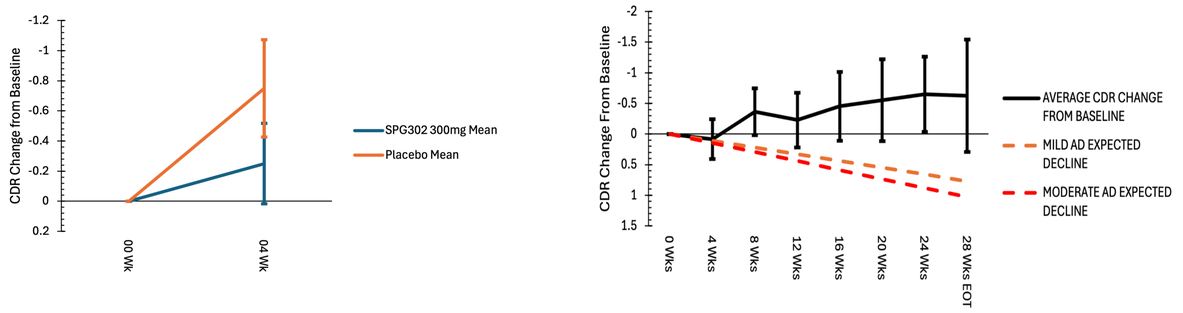


SPG302 was associated with rapid, significant and durable increases in SMMSE scores. The SMMSE is a brief cognitive test that assesses orientation, attention, memory, language, and visuospatial skills. While a score of 24 or more generally suggests normal cognition, scores below that can indicate varying degrees of cognitive impairment. In the first 4 weeks of DBPC, SPG302 increased SMMSE scores by > 2 pts. Typically, SMMSE scores decline by an average of 2 to 4 points per year (shown in the red dashed line). All patients showed a notable increase that was durable.

Efficacy – CDR-SB

CDR-SB 4-week placebo-controlled period

CDR-SB 24-week open period (weeks on treatment)



SPG302 was associated with improvements in CDR-SB. The Clinical Dementia Rating Sum of Boxes (CDR-SB) score is an FDA-approvable endpoint used to assess the severity of dementia. The annual rate of change in CDR-SB scores can vary depending on the baseline CDR-SB stage: very mild AD (CDR 0.5), ~ 1.43 points per year; mild-moderate AD (CDR 1), ~ 1.91 points per year (SE = 0.07). SPG302 treatment in all individuals showed a stabilization that was durable over time.

SPG302 treatment was associated with rapid and significant improvements in SMMSE and CDR-SB measures, supporting the hypothesis that synaptic regeneration may improve symptoms in AD.

Conclusions

- **SPG302 was generally safe and well tolerated**
- **Evidence of rapid improvement (SMMSE) within a 4-week placebo-controlled period is consistent with observations of rapid efficacy in preclinical models**
- **Durable improvements in both SMMSE and CDR-SB**
- **These early Phase 2a efficacy comparisons show competitive improvements in MMSE and CDR vs current standard of care therapies.**
- **Early results support the hypothesis that synaptic regeneration may be efficacious in restoring cognitive function in AD**
- **SPG302 is also currently being evaluated in Phase 2a trials for ALS (NCT05882695) and schizophrenia (NCT06442462).**

Database lock is underway and additional data will be presented at CTAD Dec 2025.

Acknowledgements

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