

Preliminary Analysis of the Phase 2 Trial for Rapamycin Effects on Alzheimer’s Disease and Cognitive Health (REACH)



Valentina R. Garbarino^{1,2}; Rose Ann Barajas^{1,2}; Karl Li^{1,2}; Chen-Pin Wang^{1,2}; Veronica Galvan Hart³; Amy Saklad^{1,2}; Monica Goss^{1,2}; Samuel Guess^{1,2}; Lakshmi Cherukuwada^{1,2}; Erika Zapata^{1,2}; Jessica Zapata^{1,2}; Mayuresh P. Chaudhari^{1,2}; Carlos A. Gaona^{1,2}; Angel G. Velarde^{1,2}; Katherine Guillen¹; Larissa Werneck¹; Vinu Philip^{1,2}; Cynthia Cornejo^{1,2}; Maryam Bahadori^{1,2}; Ashley LaRoche^{1,2}; Vanessa M. Young^{1,2}; Julie M. Parker-Garza^{1,2}; Daniel McCarthy^{1,2}; Joy Zeynoun^{1,2}; Noor Imran^{1,2}; Floyd A. Jones^{1,2}; Arash Salardini^{1,2}; Jordan Grow^{1,2}; Sidath C. Kumarapperuma^{1,2}; Eduardo Zilli^{1,2}; Gabriel de Erausquin^{1,2}; Sarah E. Savoia^{1,2}; Sara Doyle^{1,2}; Rebecca Hoyumpa^{1,2}; Pavel Rodriguez^{1,2}; Mitzi M. Gonzales⁴; Tiffany F. Kautz^{1,2}; Ellen Kraig²; Peter Fox²; Dean L. Kellogg Jr.^{1,2}; Sudha Seshadri^{1,2}

1. Glenn Biggs Institute for Alzheimer’s & Neurodegenerative Diseases, San Antonio, TX, USA; 2. The University of Texas Health Science Center at San Antonio; San Antonio, TX, USA; 3. Center for Geroscience and Healthy Brain Aging, The University of Oklahoma, Oklahoma City, OK; 4. Cedars-Sinai Medial Center, Los Angeles, CA

Preliminary results from the first placebo-controlled clinical trial of Rapamycin (Sirolimus®) 1mg daily for 1 year in individuals with early stage Alzheimer’s disease indicate safety, tolerability, and feasibility. Preliminary analyses of pre/post cognitive function, metabolic and blood outcomes indicate early treatment effects do not persist into post-treatment follow-up.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES & ACKNOWLEDGEMENTS
- Randomized 8-weeks of 1 mg/day rapamycin showed safety in adults (70-93 years old)¹ - Phase I open-label trial in AD indicated safety and tolerability² - We conducted the first phase II double-blind placebo-controlled study of rapamycin in an AD population Clinical Trials ID: NCT04629495 Recruitment:	Study Design: Inclusion Criteria: 55-89 years old - MCI/AD (CDR: 0.5-1) Primary Outcomes: - Adverse Events (AEs) - Safety: Change in labs Experimental Outcomes: - CNS penetration of rapamycin in whole blood - Changes in cognition, functional status, neuropsychiatric symptoms, Aβ pathology, cerebral glucose metabolism, brain volumetry - Generalized Estimation Equation Analyses, repeated treatment and timepoint effects	<u>Cohort Demographics:</u> 72 yo ± 7.8 SD; 56% Female, 22.5% Hispanic, 2.5% Black; baseline measures balanced across treatment arms <u>Primary Outcomes:</u> AEs: 59 total, (76% of IP vs. 61% of placebo participants experienced an AE p= 0.298) Labs: Mean Corpuscular Volume (MCV) steeper increase in IP arm (β = 0.135/mon, p = 0.0382), not clinically significant. <u>Experimental Functional Outcomes:</u> HVLT-R Delayed Recall: Treatment effect observed during 6 months of treatment initiation (0.3245/mo, p= 0.0226); slope difference did not persist during follow-up (p=0.0892)	- Rapamycin treatment of 1 mg/day for 12 months is safe, well tolerated and feasible in a cognitively impaired population. - Reported Adverse Events deemed possible or probably related were all previously reported side effects of rapamycin. - Ongoing analyses will evaluate changes in cognition, brain volumetry/metabolism, CNS penetrance, peripheral levels of inflammation and pathology in serum and CSF. ADVERSE EVENT CAUSALITY	1. Kraig E, et al. A randomized control trial to establish the feasibility and safety of rapamycin treatment in an older human cohort: Immunological, physical performance, and cognitive effects. <i>Exp Gerontol.</i> 2018 May;105:53-69. 2. Gonzales MM, Garbarino VR, <i>et al.</i> Rapamycin treatment for Alzheimer's disease and related dementias: a pilot phase 1 clinical trial. <i>Commun Med.</i> 2025 May 20;5(1):189. <u>Acknowledgements:</u> - Alzheimer’s Association Part the Cloud Foundation - South Texas ADRC (5T-P30-AG066546-03) - Texas Alzheimer’s Research and Care Consortium, Junior Investigator Research Grant (1541871) - Alzheimer’s Association New Investigator Award (1446397) - Institute for Integration of Medicine and Science/Clinical and Translational K12 Award (TR004529) CONTACT INFORMATION Valentina R. Garbarino Garbarino@uthscsa.edu BiggsInstitute.org ALZHEIMER’S ASSOCIATION