OC8 - A phase 2b clinical trial of neflamapimod in dementia with Lewy bodies designed to confirm the efficacy results from phase 2a

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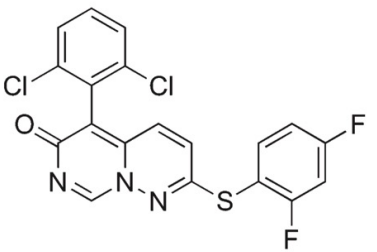
Clinical Trials on Alzheimer's Disease

Disclosures

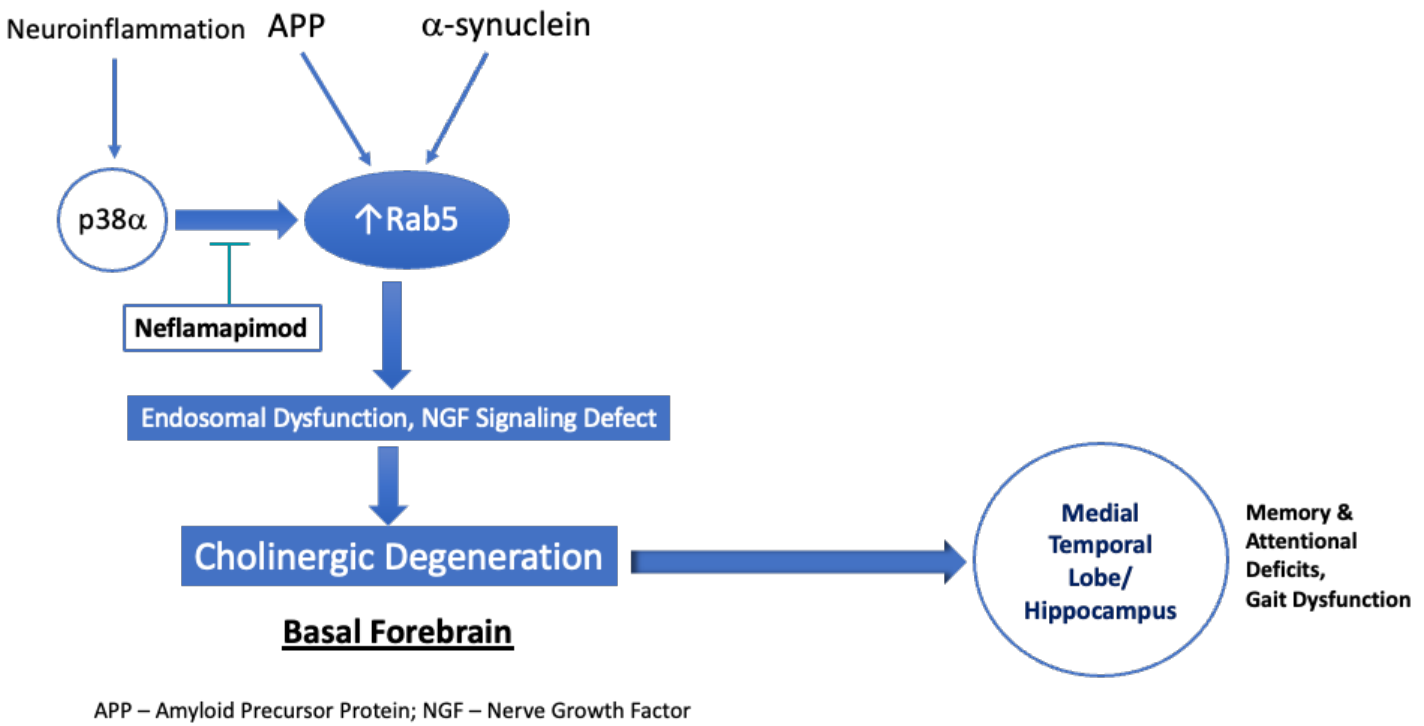
- Dr. Prins is CEO and co-owner of Brain Research Center, The Netherlands. He is also a consultant to Aribio, Eli-Lilly, and Janssen and received a speaker fee from Biogen.
- Dr. Alam is CEO of, Ms. Blackburn is a full-time employee of, and Ms. Gardner and Dr. Chu are consultants/contractors to CervoMed Inc. EIP Pharma, the corporate sponsor of the clinical trials of neflamapimod, is a wholly owned subsidiary of CervoMed.
- Dr. Galvin has no disclosures to report

Neflamapimod Background



- Oral small molecule highly selective inhibitor of the protein kinase p38α, a major activator of the cellular stress response
- In preclinical studies, reverses neurodegenerative process in basal forebrain
- Safety profile well defined, with clinical safety data in greater than 300 study participants
- Prior phase 2 studies in AD demonstrated blood-brain-barrier penetration and target engagement (reduction vs. placebo of CSF levels of p-tau and total tau)
- In dementia with Lewy bodies (DLB), in phase 2a neflamapimod improved versus placebo cognitive, functional and motor aspects of the disease

Neflamapimod Treatment Targets Basal Forebrain Cholinergic Degeneration



Alam & Nixon, *Molecular Degeneration,* 2023

AscenD-LB demonstrated neflamapimod improved cognition and function in DLB

Outcome	Measure	40mg BID + 40mg TID		40mg TID	
		Mean vs. placebo (95% CI)	p-value	Mean vs. placebo (95% CI)	p-value
Dementia Severity	Clinical Dementia Rating Sum of Boxes (CDR-SB)	-0.45 (-0.83, -0.06)	0.023	-0.56 (-0.96, -0.16)	0.007
Cognition	Neuropsychological Test Battery (NTB) Composite z-score	0.04 (-0.11, 0.19)	>0.2	0.17 (0.00, 0.35)	0.049
	Attention Composite z-score	0.14 (-0.06, 0.35)	0.17	0.28 (0.04, 0.51)	0.023
Motor Function	Timed and Go Test (TUG)	-1.4 (-2.7, -0.1)	0.044	-1.4 (-2.6, -0.2)	0.024

On-study (all time-points) results; change from baseline analysis utilizing Mixed Model for Repeated Measures (MMRM)
Number of participants: 41 for placebo, 20 each for 40mg BID and 40mg TID

***Nature Communications*, 13, Article number: 5308 (2022). https://www.nature.com/articles/s41467-022-32944-3**

Objective of Presentation

Detail the major learnings from the Phase 2a AscenD-LB in DLB, as well MRI results from a prior phase 2a study in AD, that were incorporated into the final design of the ongoing Phase 2b RewinD-LB Study

AscenD-LB

- Phase 2a Exploratory Study
- Results Published:
  - Jiang et al, *Nature Communications,* 2022
  - Alam et al, *Neurology*, 2023

RewinD-LB

- Phase 2b study designed to confirm the phase 2a efficacy findings
- First patient dosing occurred August 2023
- Completion of enrollment planned for H1’24

Patient Population

AscenD-LB Inclusion Criteria Identified Robust DLB Patient Population

Inclusion criteria:

- Probable DLB by 2017 consensus criteria (dementia, with at least one core clinical feature of DLB)
- Demonstrated abnormality in dopamine uptake by DaTscan™ (Ioflupane I123 SPECT)]
- MMSE 16-28

Patients enrolled had attentional deficits, with >1.5 SD deficits vs. age-adjusted norm in One Back - accuracy, Identification and Detection tests

  - Lesser decline in executive function, with ≤1 SD deficit in Letter Fluency and Category Fluency; consistent with the literature for mild DLB

Baseline Disease Characteristics		Baseline z-score[1] on tests within NTB	
CDR 0.5/1.0/2.0	37%/52%/11%	Identification	-1.6 (1.6)
MMSE	23.0 (3.6)	Detection	-1.6 (1.6)
Fluctuating cognition	61%	One back (accuracy)	-2.6 (1.6)
Visual hallucinations	58%	One card learning	-1.1 (0.8)
REM sleep disorder	66%	Letter Fluency	-0.7 (1.0)
Parkinsonism	81%	Category Fluency	-1.0 (1.4)
≥2 features	85%		

[1] z-score relative to age adjusted norm; NTB — Neuropsychological Test Battery

AscenD-LB results stratified by presence of AD Co-Pathology (by plasma ptau181 levels)

- Efficacy results analyzed after stratification presence (46%) of patients in study) or absence (54%) of AD co-pathology at study entry, as assessed by prospectively defined cut-off for plasma ptau181
  - Analysis by presence/absence of AD co-pathology pre-specified in protocol
  - Ptau181 cut-off prospectively defined from an independent cohort in patients with AD

RESEARCH ARTICLE OPEN ACCESS

Association of Plasma Phosphorylated Tau With the Response to Neflamapimod Treatment in Patients With Dementia With Lewy Bodies

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Patients in Phase 2a without AD Co-pathology show substantial response to neflamapimod

AscenD-LB

	Overall Study Population				Patients Without AD Co-pathology (Plasma ptau181 < cutoff)			
	N= NFMD TID, Placebo	Difference[1] (95% CI)	*p*-value	Cohen's *d* Effect size	*N*= NFMD TID, Placebo	Difference[1] (95% CI)	*p*-value	Cohen's *d* Effect size
NTB	19,37	+0.17 (0.00,0.35)	0.049	0.47	11,19	+0.21 (-0.07,0.49)	0.13	0.56
Attention	19,36	+0.28 (0.04,0.51)	0.023	0.41	11,18	+0.42 (0.07,0.78)	0.023	0.78
CDR-SB	20,38	-0.56 (-0.96,-0.16)	0.007	0.31	11,22	-0.60 (-1.04,-0.06)	0.031	0.74
TUG	20,38	-1.4 (-2.6,-0.2)	0.024	0.50	11,20	-3.1 (-4.7,-1.6)	<0.001	0.74
ISLT	20,42	+0.32 (-0.48,1.12)	NS	0.15	11,22	+2.1 (0.0,4.2)	0.053	0.55
ISLT - RECOGNITION	19,39	+0.47 (-0.17,1.11)	0.15	0.17	10,21	+1.4 (0.02,2.5)	0.024	1.0

[1] Difference between neflamapimod and placebo.

NTB: Neuropsychological Test Battery (6-test cognitive test battery); ISLT – International Shopping List Test. Improvement reflected by negative sign for CDR-SB and TUG and positive sign for other measures. By convention Cohen's d 0.2-0.4=small effect, 04-0.8=moderate, ≥0.8=large

Clinical Endpoints

Performance of Clinical Endpoints in AscenD-LB

- Clinical endpoints that can detect effects on both cognitive and motor function (specifically, CDR-SB and TUG) performed better in the trial with respect to detecting improvement over placebo than endpoints that are purely focused on evaluating cognition
- Underperformance of Neuropsychological Test Battery(NTB) attributable to:
  - Ceiling effects, as all patients receiving cholinesterase inhibitors, while the NTB was modeled after a cognitive test battery that showed responsiveness to treatment in a study of rivastigmine
  - Modest level of deficits of executive function at baseline, tests for which were a major component of the NTB

Clinical Trial Simulations to Estimate Statistical Power of Individual Endpoints

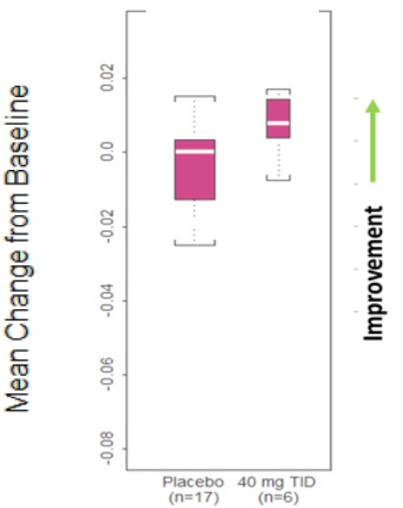
- Sample size for RewinD-LB was evaluated by power analysis via clinical trial simulations:
  - Data in AscenD-LB for the major clinical endpoints in the neflamapimod 40mg TID and placebo groups in patients *without* AD co-pathology was utilized to generate for each patient a change from baseline for each endpoint at individual visits over the course of each of the simulated clinical study
  - The result of each simulated clinical trial was analyzed by utilizing the linear mixed effects model for repeated measures (MMRM) that will be utilized to analyze RewinD-LB
- Based on the simulation of 100 clinical trials with 80 patients per treatment group, and assuming a 10% dropout rate, there is ~85% power with the NTB, 95% power with TUG, and >95% power with CDR-SB (approaching 100%) to detect a treatment effect at an alpha level of 0.05

Biomarkers

EEG Effects in AscenD-LB Study

- Baseline and end-of-treatment EEGs obtained in 29 patients (17 placebo, 6 neflamapimod 40mg BID, 6 neflamapimod 40mg TID)
  - Covid19 pandemic prevented obtaining EEGs in all patients
- No differences between neflamapimod and placebo in spectral analysis
  - Potentially confounded by all patients receiving cholinesterase inhibitors
- Significant dose-dependent increase vs,, placebo in beta band seen in functional connectivity analysis
  - Beta band power previously identified as strongest discriminator between DLB and AD (Dauwan, 2016, Mehraram, 2020)

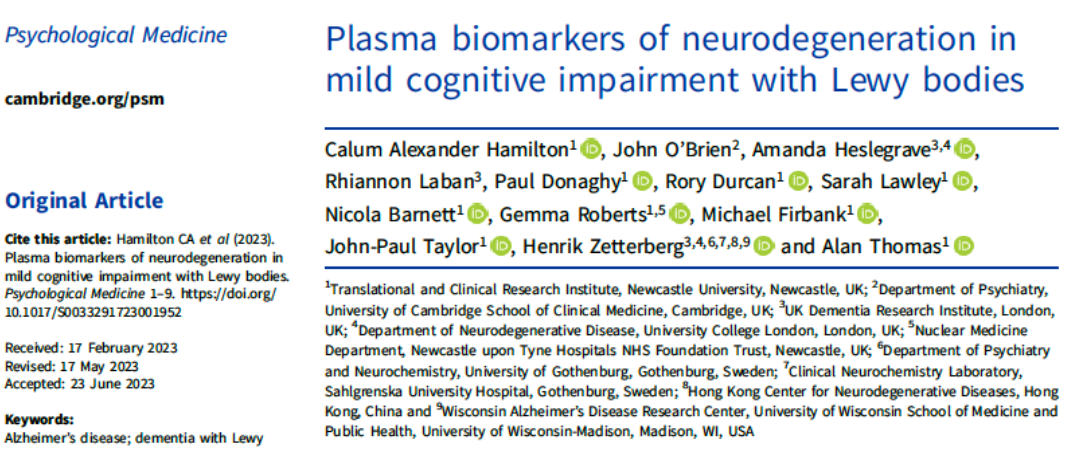
Increased Beta Functional Connectivity on EEG



Mean Functional Connectivity AECc in the **beta** band (13-30 Hz) significantly increased with neflamapimod TID (n=6) vs all placebo (n=17) (p=0.03) and vs placebo TID (n=6) (p=0.01).

CSF and Plasma Biomarkers in DLB

- No CSF or plasma biomarkers specific have been reported
- AD biomarkers (e.g., plasma ptau) may be elevated, but generally tracks with co-pathology
- Recent report (right) indicated that both glial fibrillary acidic protein (GFAP) and neurofilament light chain (NfL) can differentiate MCI due to Lewy bodies from healthy controls, with GFAP being more discriminant



Psychological Medicine

cambridge.org/psm

Original Article

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Alzheimer's disease; dementia with Lewy bodies; mild cognitive impairment;

Plasma biomarkers of neurodegeneration in mild cognitive impairment with Lewy bodies

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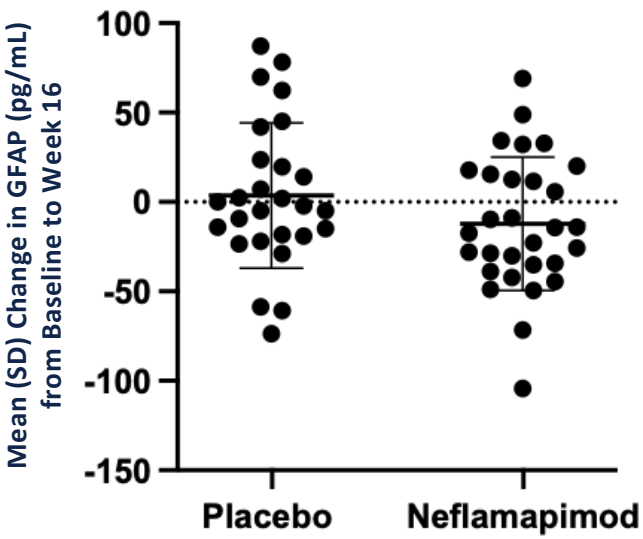
Neflamapimod Reduced GFAP Levels vs. Placebo in Patients without AD Co-Pathology

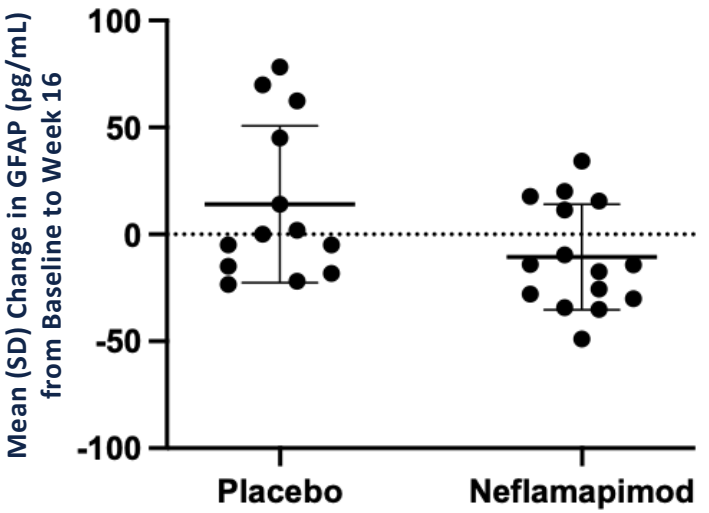
AscenD-LB

Overall Study Population



Mean 3.7 pg/mL increase in placebo vs. mean 12.3 pg/mL reduction with NFMD, p=0.13 for difference

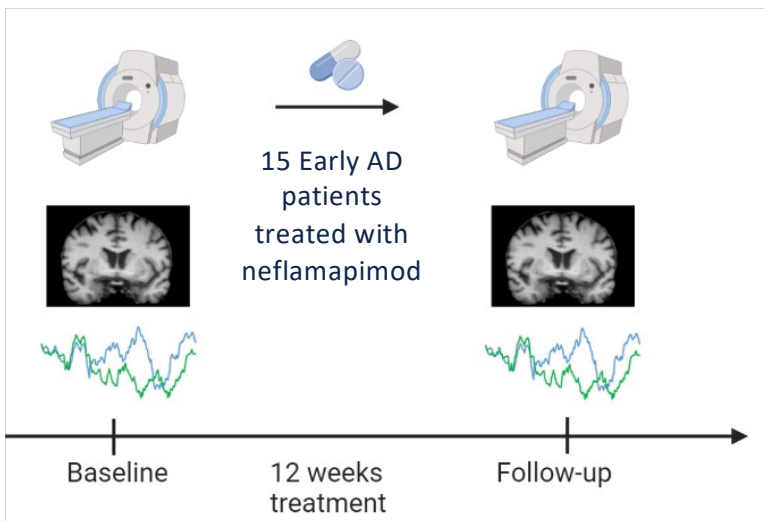
Patients < ptau181 cut-off for AD Co-Pathology

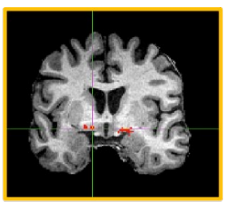


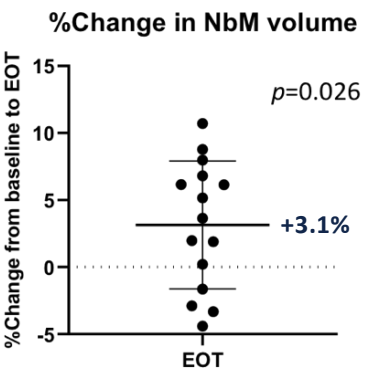
Mean 14.1 pg/mL increase in placebo vs. mean 10.6 pg/mL reduction with NFMD, p=0.04 for difference

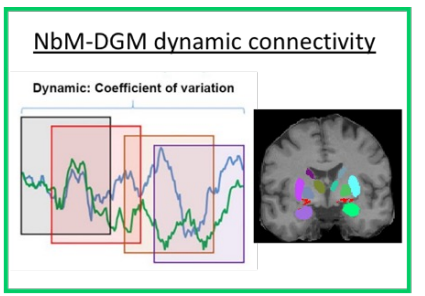
Potential Effect on Basal Forebrain Atrophy in Prior Phase 2a Study in AD

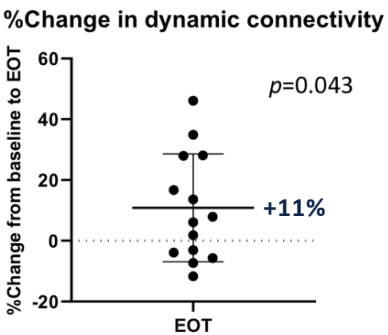
Neflamapimod treatment is associated with increased basal forebrain volume and functional connectivity











NbM – Nucleus basalis of Meynert; DGM – Deep Grey Matter

Lin C-P, Noteboom S, Bet M, Alam J, Prins N, Barkhof F, Jonkman L, Schoonheim M, Oral Presentation at AD/PD™ 2023, Gothenburg, Sweden, 1 April 2023

Summary

Summary

- With incorporation of DaTscan, 2017 diagnostic criteria successfully identified a robust DLB patient population with prominent attentional deficits
  - Executive function deficits less prominent in early stage DLB
- CDR-SB is the optimal primary endpoint for phase 2b
- The exclusion of patients with AD co-pathology substantially increases the magnitude of the treatment effect vs. placebo
- Clinical trial simulations indicate that with CDR-SB as primary endpoint and the exclusion of patients AD co-pathology phase 2b study has > 95% statistical power (approaching 100%) to meet its primary endpoints
- Potential Biomarker Effects Identified:
  - Beta functional connectivity on EEG
  - Basal forebrain atrophy and functional connectivity by MRI
  - Plasma GFAP; additional plasma stored for analysis as additional biomarkers are developed

PARTICIPANTS

- DLB by consensus criteria, including abnormal DaTscan™
- Global CDR score of 0.5 or 1.0
- No AD co-pathology, assessed by plasma ptau181

RewinD-LB

INTERVENTION

- Randomized on a blinded basis 1:1 to neflamapimod 40mg capsules (n=80) or matching placebo capsules (n=80), TID for 16 weeks, followed by 32-week open-label neflamapimod extension treatment

OUTCOME MEASURES

- Primary: Clinical Dementia Rating Sum of Boxes (CDR-SB)
- Secondary: Timed Up and Go (TUG) test, Neuropsychological Test Battery (NTB), Clinical Global Impression of Change (CGIC)
- Tertiary: Cognitive fluctuation scale, 12-item Neuropsychiatric Inventory (NPI-12), Part 3 of MDS-Unified Parkinson's Disease Rating Scale (UPDRS)
- EEG: beta functional connectivity (primary), eyes-closed to eyes-open alpha reactivity
- MRI: atrophy of basal forebrain, and its functional connectivity

https://clinicaltrials.gov/study/NCT05869669

RewinD-LB Clinical Sites

Investigator Name	Site	Location
Liana Rosenthal, MD	Johns Hopkins University	Baltimore, MD
Matthew Barrett, MD	Virginia Commonwealth University	Richmond, VA
Andrea Bozoki, MD	University of North Carolina	Chapel Hill, NC
Irene Litvan, MD	UCSD	San Diego, CA
Daniel Huddleston, MD	Emory	Atlanta, GA
Paraunyou Julayanont, MD	Barrow Neurological Institute	Phoenix, AZ
Artin Minaeian, MD	SC3 Research Group	Pasadena, CA
Rajesh Pahwa, MD	KUMC	Kansas City, KS
Linda Pao, MD	JEM Research Institute	Lake Worth, FL
Kathryn Bradley, MD	Banner Alzheimer's Institute	Tucson, AZ
Bradley Boeve, MD	Mayo Clinic	Rochester, MN
Lawrence Honig, MD, PhD	Columbia	New York, NY
Stephen Gomperts, MD, PhD	Massachusetts General Hospital	Charlestown, MA
Babak Tousi, MD	Cleveland Clinic	Cleveland, OH
Douglas Scharre, MD	OSU	Columbus, OH
Jori Fleisher, MD	Rush University Medical Center	Chicago, IL
Sharon Sha, MD	Stanford	Palo Alta, CA
Samatha Holden, MD	University of Colorado	Aurora, CO
Daniel Murman, MD	University of Nebraska Medical Center	Omaha, NE
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Magdelena Tolea, PhD	University of Miami	Miami, FL
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Aaron Ritter, MD	Hoag Memorial Hospital	Newport Beach, CA
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Joseph Cahill, MD	Panhandle Research, LLC	Pensacola, FL
Angela Traylor, MD	Tandem Clinical Research	Marrero, LA
Anwar Ahmed, MD	Advent Health	Orlando, FL
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Prof. Dag Aarsland	Kings College	London, England, UK
Dr Saif Sharif	MARC	Hampshire, England, UK
Dr. Manpreet Kaur	Re:Cognition Health	London, England, UK
Dr Robert Barber	U of Newcastle	Newcastle, England, UK
Prof John O'Brien	Cambridgeshire and Peterborough NHS Trust	Cambridgeshire, England, UK
Dr Simon Vann Jones	U of Exeter Cornwall Partnership NHS Foundation Trust	Redruth, England, UK

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