CYP46A1 activation by low-dose efavirenz enhances brain cholesterol metabolism in subjects with early Alzheimer's disease

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SUPPLEMENTAL METHODS

Inclusion and Exclusion Criteria

Inclusion criteria for patient recruitment were as follows: age of 55-85; male or female; diagnosed with Mild Cognitive Impairment (MCI) or early dementia due to AD as defined by complaint of cognitive decline, the Mini-Mental State Exam (MMSE) score between 16 and 30, and the Cognitive Dementia Rating (CDR) between 0.5-1 [1, 2]. Other inclusion criteria were: education of more than 8 years; literate in English, and/or good working history that precluded consideration of mental retardation; visual and auditory acuity sufficient for neuropsychological testing; modified Hachinski Ischemic Score of less than 4 [3]; no major health issues or diseases expected to interfere with the study; willingness to complete all assessments and study procedures; not being pregnant, lactating or of child-bearing potential (women had to be >2 years post- menopausal or surgically sterile); if cognitively impaired, then have a study partner in frequent contact with the subject and willing to accompany them to visits and complete partner study forms; no contraindication or hypersensitivity to EFV; screening laboratory testing must be within normal limits or, if abnormal, must be judged to be clinically insignificant by the investigators; and use of a cholinesterase inhibitor and statin medication (except simvastatin, which seems to cross the blood-brain barrier and thus could inhibit brain cholesterol biosynthesis), if doses were stable for 3 months prior to enrollment.

The study exclusion criteria were: any CNS disease other than suspected prodromal or early AD, such as clinical stroke, brain tumor, normal pressure hydrocephalus, brain tumor, multiple sclerosis, significant head trauma with persistent neurological or cognitive deficits or complaints, Parkinson's disease, frontotemporal dementia or other neurodegenerative diseases; ongoing major and active psychiatric disorder and/or other concurrent medical condition that, in the opinion of

the investigator, might compromise safety and/or compliance with study requirements; current suicidal ideation or history of suicide attempt; history of alcohol or other substance abuse or dependence within the past two years; any significant systemic illness or unstable medical condition that could affect study compliance, including a history of prolonged QTc; laboratory abnormalities in B_{12}, TSH, or other common laboratory parameters that might contribute to cognitive dysfunction; current use of medications with psychoactive properties (e.g., anticholinergics, antihistamines, antipsychotics, sedative hypnotics, anxiolytics) that, in the opinion of the investigator, might deleteriously affect cognition; use of other investigational agents one month prior to entry and for the duration of the study; treatment with any of the following agents/classes within the past 3 months: simvastatin; antiepileptic agents, clopidogrel, voriconazole, systemic ketoconazole, cyclosporine, St. John's Wort.

SUPPLEMENTAL RESULTS

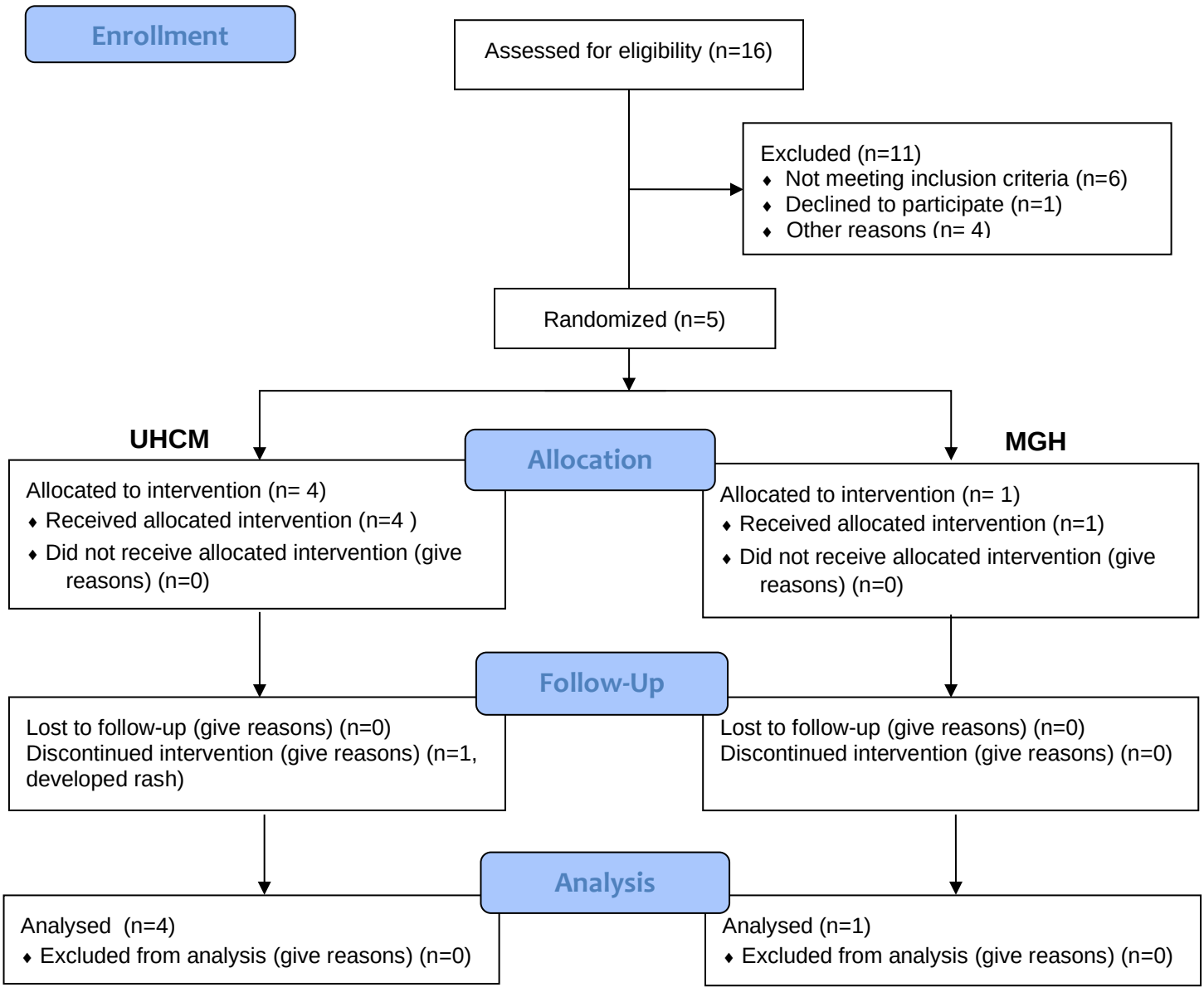
Supplemental Table 1. Summary of visits and evaluations common for both clinical sites and specific for the MGH site. SC, screening visit; BL, baseline visit; PC, phone call; CV, clinic visit; DC, early discontinuation visit; W, week; *, MGH site only; ** unscheduled visit; 24HC, 24-hydroxycholesterol.

Evaluations	SC	BL W 0	PC W 2	CV W 4	PC W 6	CV W 8	PC W 10	CV W 12	PC W 14	CV W 16	PC W 18	CV W 20	CV W 22	DC **
Administrative														
Eligibility Confirmation, Informed Consent, Demographics, Randomization, Participant ID Assignment	x													
Efavirenz Dispensing, Management and Return Log		x		x		x		x		x		x		x
Concomitant Medications Log	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Confirm Study Drug compliance		x		x		x		x		x		x		
Protocol Deviation Log	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Safety and Tolerability														
Height, Weight & Vital Signs	x	x		x		x		x		x		x	x	x
Medical, Surgical, Family & Social History	x													
Adverse Events/Active Conditions	x	x	x	x	x	x	x	x	x	x	x	x	x	x
12-Lead EKG	x							x					x	x
CDR (Clinical Dementia Rating)	x											x		
MMSE (Mini-Mental Status Exam)	x													
MoCA (Montreal Cognitive Assessment)		x										x		
Modified Hachinski Ischemia Score	x													
NPI-Q (Neuropsychiatric Inventory)	x					x				x		x	x	x
Suicidality: Baseline Suicidality Assessment	x	x												
Suicidality: Since Last Suicidality Assessment		x		x		x		x		x		x	x	x
Neurological & Physical Examination	x					x						x	x	x
Symptom Checklist		x	x	x	x	x	x	x	x	x	x	x	x	x
Safety Labs: Fasting CMP (Ca, BUN, Cr, AST, ALT, Bilirubin)	x					x		x		x		x	x	x
Safety Labs: Fasting CBS with differential & Lipid Panel	x			x		x		x		x		x	x	x
Safety Labs: B12 & TSH	x													
Safety Labs: Urinalysis	x												x	x
Safety Labs: PT-INR (Prothrombin Time & International Normalized Ratio		x										x		
Lumbar Puncture		x										x		
Urinalysis	x												x	x
Initial Serious Adverse Events Report			x	x	x	x	x	x	x	x	x	x	x	x
Follow-Up Serious Adverse Events Report			x	x	x	x	x	x	x	x	x	x	x	x
Deuterated Water Dispensing for Seven Days*		x								x				
Outcomes														
Plasma: Total Cholesterol & 24HC		x		x		x		x		x		x	x	
CSF: Total Cholesterol, 24HC, Aβ40, Aβ42, Total Tau, Phosphotau		x										x		
SILK Study Plasma: deuterated 24HC*		x		x		x		x		x		x	x	
SILK Study CSF: deuterated 24HC*		x										x		
DNA Genotyping		x												

CONSORT

TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



Supplemental Fig. 1. A tree showing the screening, enrollment, randomization, and outcome of subjects in the efavirenz clinical trial. UHCMC, Brain Health and Memory Center and the Memory Disorders Clinic in Cleveland, OH; MGH, Alzheimer's Clinical & Translational Research Unit at Massachusetts General Hospital.

RFERENCES

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