Effects of Montelukast Therapy on Alzheimer's Disease (EMERALD)

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PROTOCOL

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PRÉCIS

Study Title

Effects of Montelukast Therapy on Alzheimer's Disease

Acronym

EMERALD

Objectives

Our *primary objective* is to determine the safety, dose-response and target engagement of the treatment with escalating doses of Montelukast in those with mild cognitive impairment (MCI) or early Alzheimer's disease (AD) dementia.

Our *secondary objectives* are to assess the efficacy and estimate the effect size of up to 1-year treatment of Montelukast on biomarkers of neurodegeneration and cognition in MCI/early AD dementia.

Design and Outcomes

This is a double-blind placebo-controlled randomized clinical trial that compares Montelukast to placebo in individuals with MCI and early AD dementia. Our measures include cognitive function, CSF biomarkers and neuroimaging (cerebral perfusion and markers of vascular brain damage).

Interventions and Duration

The intervention includes Montelukast (10, 20, or 40 mg) or placebo. The duration of the study is 1 year.

Sample Size and Population

Our target population includes subjects who are 50 years or older with MCI and early AD dementia. Our sample size is 30 for this trial.

TABLE 1. SCHEDULE OF PROCEDURES FOR THE DURATION OF THE STUDY

Phase:	SCREEN	BASELINE		FOLLOW-UP			
Number of visits	1-2[@]	1-2		4-5			
Months	-1	0		1.5	3	6	12
Informed Consent	X						
Cognitive screening	X						
Screening labs	X*						
CSF for biomarker and molecular analysis		X**					X^
Weight/Height	X	X	RANDOMIZATION	X	X	X	X
Blood Pressure	X	X		X	X	X	X
Safety labs				X[#]	X[#]	X[#]	X[#]
Brain MRI		X					X
Vascular function measures (PWV/PWA)		X					X
Cognitive Battery		X				X	X
Functional battery (FAQ, IADL, SPPB)		X***					X
LTE_4 testing		X				X	X
Blood for biospecimen banking		X				X	X
Time (in minutes)	60-120	150-210		30	30	120-150	120-150

*: Screening labs include: CBC, CMP (BUN, Cr, electrolytes, liver function test (LFT)), B12, TSH and PT/INR.
**: If subject has had a lumbar puncture (LP) within the 6 months prior to their screening/baseline visit and samples are available for measuring CSF outcomes, then no LP will be done at baseline. Otherwise, LP will be done at baseline to obtain CSF for outcome measures.
***: FAQ will be skipped at baseline if already done at screening visit.
#: Safety labs at 6 weeks, 3, 6 and 12 months include CBC, CMP (BUN, CR, electrolytes, liver function test).
^: If subject did not have PT/INR done at baseline or started taking any blood thinners during the study, PT/INR will be done before LP at 12 months.
@: for subjects who are consented electronically and complete a portion of the screen visit virtually, a 2nd in-person visit will be conducted for parts of the screen visits that cannot be done remotely.

1. STUDY OBJECTIVES

Our primary objective is to determine the safety and dose-response for and target engagement of the treatment with escalating doses of Montelukast in those with mild cognitive impairment (MCI) or early Alzheimer's disease (AD) dementia based on cognitive and functional evaluation.

Our secondary objectives are to assess the efficacy and estimate the effect size of up to 1-year treatment of Montelukast on biomarkers of neurodegeneration and neuro-inflammation, and vascular function; and to estimate the effect of Montelukast on cognitive function, functional measures, and vascular inflammatory and endothelial markers in MCI/early AD dementia.

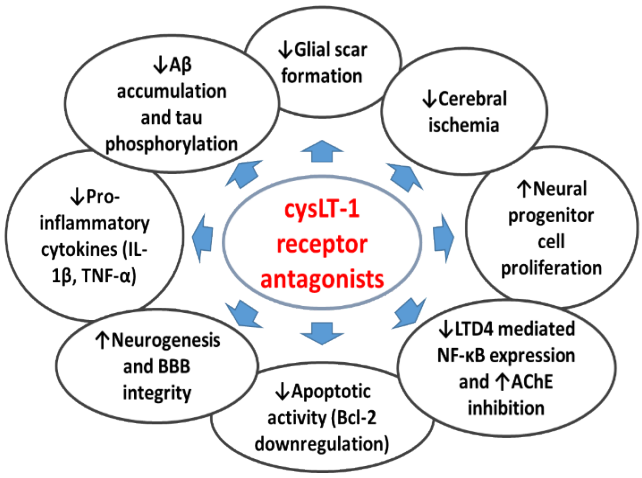
2. BACKGROUND AND RATIONALE

Therapeutic options for AD remain limited, especially treatments linking neurovascular and neuro-inflammatory changes with clinical manifestations of disease.[1] Prior research studies have documented a positive effect of cysteinyl leukotriene type 1 (cysLT-1) receptor antagonist, particularly Montelukast, on neuro-inflammatory processes and neuronal injury, blood brain barrier (BBB) integrity, and amyloid-β42 (Aβ) accumulation. Although Montelukast is currently in use for the treatment of inflammatory diseases e.g. bronchial asthma and exercise-induced bronchospasm, its effect on cognitive function and AD biomarkers however, is yet to be fully understood.

2.1. DISEASE TARGETS FOR CYSTEINYL LEUKOTRIENE INHIBITION IN AD

AD is a multifaceted neurodegenerative disease with pathologic hallmarks of extracellular plaques and neurofibrillary tangles, containing hyperphosphorylated tau and Aβ proteins, respectively. Cysteinyl leukotrienes, cysLTs (LTC_4, LTD_4, LTE_4), are pro-inflammatory and immune modulating lipid mediators of the 5-lipoxygenase (5-LOX) pathway, which via activation of receptors, cysLT-1R and cysLT-2R, target vascular, neuro-inflammatory and amyloid pathways involved in AD initiation or progression.[2,3] Neuromodulatory targets of receptor-specific (cysLT-1R) leukotriene receptor antagonists (LTRA) are shown in **Figure 1**. Extensive *in vivo* and *in vitro* animal studies have demonstrated that Aβ peptide accumulation results in upregulation of cysLT-1R expression.[4] This in turn, increases pro-inflammatory chemokines and cytokines such as NF-κB, tumor necrosis factor (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and activation of pro-apoptotic protein caspase-3, downregulation of anti-apoptotic protein Bcl-2, and microglial activation.[5-7] IL-1 has been implicated via activated microglia, in the neural expression and activation of acetylcholinesterase (AChE) protein, exacerbating acetylcholine decline and AD dysfunction.[4] Results of a Montelukast study on *in vitro* embryonic mice neuronal cell cultures demonstrated that Montelukast had neuroprotective effects and reversed neuro-inflammatory changes by downregulating cysLT-1R NF-κB signaling and apoptotic-related proteins.[5,8] At the neurovascular level, endothelial progenitor cells (EPC) have a potential role in repairing the BBB endothelium[9,10] by differentiating into BBB like-cells[11,12] and improving neurovascular healing.[13] EPC are decreased in AD patients and correlate positively with cognitive function.[14] Moreover, cysLTs induce BBB disruption and leakage, and consequent brain edema.[15] CysLT-1R is also highly expressed in microvascular

Figure 1. Neuromodulatory targets of cysLT-1 antagonists



endothelium following brain injury in rats and humans.[16,17] In adult rat neural progenitor cells, blockade of cysLT-1 and GPR17 receptors was found to increase neural stem and progenitor cell proliferation, suggesting a potential for neurogenesis and restoration of BBB integrity.[18] Previous work suggests that CysLT-1R antagonists attenuate cerebral ischemia, reduce astrocytic proliferation and glial scar formation, and restore microvascular endothelial function.[19,20] In MCI and AD, inhibition of cysLT-1R signaling may translate into improved cognition. This multi-target characteristic of CysLT-1R antagonists increases the likelihood of producing a disease-modifying effect for prodromal and early Alzheimer's disease.

2.2. SAFETY OF RECEPTOR-SPECIFIC LTRA IN MCI AND EARLY AD

Multiple research studies have shown that Montelukast has a good safety profile with respect to adverse events.[21] In placebo-controlled dose-ranging studies conducted by the Montelukast Asthma Study Group, adult participants were randomly assigned a placebo or Montelukast at daily doses ranging between 2 mg and 200 mg for the treatment of chronic asthma. Authors found that adverse events were not dose-related, and were similar between placebo and Montelukast treatment groups.[22,23] Furthermore, in a pediatric study, doses of Montelukast up to 536 mg were found to not yield any serious side effects and could be administered from home.[24] Although the US Food and Drug Administration (FDA) has issued warnings linking Montelukast and suicidality, extensive systemic reviews of Montelukast and suicidality have yielded inconclusive findings. In a post-marketing review of adverse events (AE) conducted for the FDA by Merck (116 clinical trials, n=20,131), no completed suicides were reported. In addition, suicide risk was rare and did not differ between the Montelukast and placebo groups.[25,26]

Prior animal studies in young and older rats showed improved task learning skills among older rats with learning and memory deficits and taking oral Montelukast (10mg/kg body weight).[27] A case series report of 17 study subjects with cognitive impairment who were taking 80 mg total oral daily dose of Montelukast suggested subjective memory improvement. More importantly, subjects did not report any side effects or adverse reactions for the administered Montelukast dose.[28]

2.3. STUDY RATIONALE

In the brain, cysteinyl leukotrienes bind cysLT-1R and cysLT-2R. CysLT-1 receptor inhibition decreases oxidative stress,[29] improves endothelial function and cerebral perfusion, and decreases cholinergic depletion, neuro-degeneration, and memory loss.[28,30-33] CysLT-1R antagonists affect multiple systems involved in AD including vascular and neural progenitor cell function, Aβ-triggered neurotoxicity and tau hyperphosphorylation.[18,34] CysLT-1R blockade using Montelukast, influences crucial steps in Aβ-induced cognitive decline, restoration of BBB integrity, neuronal injury and neurogenesis by inhibiting neuro-inflammation and apoptosis.[20,27] Use of Montelukast in this human trial will address knowledge gaps in long-term administration of the drug, and in its future clinical translation for AD treatment.

3. STUDY DESIGN

This is a **PHASE II**, 1-year double-blind placebo-controlled randomized clinical trial where participants will be treated with Montelukast (escalating doses: 10, 20 to 40 mg) or matched placebo. The study will enroll 36 participants to account for an expected 20% drop-out rate in order to achieve a sample size of 30 with 15 participants in each group.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1. INCLUSION CRITERIA

(1) Age: 50 years or older;

(2) MCI group will be defined based on:

(i) Subjective memory concern;

(ii) Abnormal memory function documented using the Logical Memory subscale (Delayed Paragraph Recall, Paragraph A only) from the Wechsler Memory Scale-Revised (the maximum score is 25): [<11 for 16 or more years of education; <9 for 8-15 years of education; <6 for <7 years of education];

(iii) Montreal Cognitive Assessment (MoCA) < 26;

(iv) Clinical Dementia Rating scale /Memory box score=0.5;

(v) General functional performance sufficiently preserved (Functional Assessment Questionnaire ≤5).

(3) Early AD dementia group will be defined based on:

(i) Subjective memory concern;

(ii) Abnormal memory function documented using the Logical Memory subscale (Delayed Paragraph Recall, Paragraph A only) from the Wechsler Memory Scale-Revised (the maximum score is 25): [<11 for 16 or more years of education; <9 for 8-15 years of education; <6 for <7 years of education];

(iii) Montreal Cognitive Assessment (MoCA) <26;

(iv) Clinical Dementia Rating scale/Memory box score 1 or 2;

(v) Early AD dementia defined as Functional Assessment Staging Test (FAST) of 4 or 5;

In instances where the diagnosis of early AD is not clear, a review of the subject's cognitive and non-cognitive data will be performed by the study physicians or neuropsychologists and a diagnosis of the degree of cognitive impairment will be based on the clinical judgment of the study physicians or neuropsychologists.

4.2. EXCLUSION CRITERIA

(1) Intolerance to Montelukast;

(2) Current diagnosis of bronchial asthma or exercise-induced bronchospasm **and** currently on Montelukast or other leukotriene receptor antagonists (Zafirlukast, Pranlukast);

(3) Liver disease (elevated liver enzymes (>2x normal): ALT, AST, alkaline phosphatase, total bilirubin);

(4) Renal disease (Creatinine >2.0 mg/dl), platelets<50,000/µl, or INR>1.9;

(5) Diagnosis of any neurological or psychiatric disorders that affects cognition such as uncontrolled depression, schizophrenia, Parkinson's disease or use of anti-Parkinsonian therapies (unless used for essential tremor), multiple sclerosis, or other active medical condition that in the judgment of the study physicians would affect the safety of the subject or scientific integrity of the study;

(6) Other contributing factors to cognitive impairment such as uncontrolled hypothyroidism (TSH >10 mU/l) or untreated low vitamin B12 (<250 ng/mL);

(7) Uncontrolled congestive heart failure reflected by poor exercise tolerance and shortness of breath at rest or with some exertion;

(8) Actively undergoing chemotherapy or radiation therapy for cancer treatment;

(9) History of stroke in the past 3 years;

(10) Severely impaired cognition (MoCA ≤10, FAST >5 or CDR >2);

(11) Inability to have MRI and LP e.g. for MRI, metal implants or cardiac pacemaker or for LP, bleeding diathesis from disease states or from use of anticoagulants such as warfarin, heparin and related products, Rivaroxaban or Xarelto, Apixaban or Eliquis, Edoxaban or Savaysa, Dabigatraban or Pradaxa. Subjects who can have either one LP or MRI will be enrolled;

(12) Inability to have cognitive assessment due to hearing, vision, or language issues or due to severe impairment;

(13) History of increased intracranial pressure (ICP);

(14) In those who are unable to demonstrate that they understood the details of the study using the UBACC modified for EMERALD (i.e. lack of decisional-capacity to consent), a study partner/surrogate who can sign on their behalf will be required; otherwise, they will be excluded;

(15) Use of phenobarbital or rifampin due to drug interaction.

4.3. STUDY RECRUITMENT

Potential participants will be identified through community activities, health fairs, advertisements in periodicals and local newspapers, and patient referrals. Below we describe our recruitment venues:

(1) The Emory Alzheimer's Disease Research Center (ADRC) Clinical Core registry of research participants will be utilized for recruitment. Participants have agreed to be referred to other studies.

(2) Community-based recruitment: Community education sessions in local neighborhoods e.g. churches or barbershops will be conducted, and attendees will be invited to participate in this study.

(3) MindMate App recruitment: MindMate users have the opportunity to first express their interest in clinical studies within the 'Research' section of the app. MindMate can also reach out to users once they have consistently utilized the app, usually after 3-4 weeks, and ask the user if they would like to receive further information when a matching clinical study is available in their area. All users that are interested in participating in a clinical study must then go through a multi-stage opt-in & consent process that will be conducted in-person or electronically. After MindMate matches a user to an open clinical trial, they automatically ask if they're happy to be contacted by a researcher to learn more about an open study they might qualify for.

(4) Physician recruitment: Local physicians (primary care or specialty physicians) will be informed of the study and its criteria and provided information about referral to the study personnel. In addition, flyers for the study will be posted at outpatient areas in the local medical facilities.

5. STUDY INTERVENTIONS

5.1. INTERVENTIONS, ADMINISTRATION, AND DURATION

Participants will be randomized to either Montelukast or placebo in a 1:1 fashion. All participants will be initiated on 10 mg. The dose will be increased in 2-week increments to 20 mg and 40 mg as long as participants report no intolerable symptoms or adverse events (e.g. jaundice, headache, GI symptoms, and neuropsychiatric changes), and liver enzymes checked at 6 weeks do not exceed 3X baseline levels. If participant had positive LFT change (3x increase), dose will be decreased to the prior level (20 mg or matched placebo) and LFT rechecked 2 weeks later. If LFT increases further, then dose will be decreased to 10 mg or matched placebo. If LFT are still increased 2 weeks after 10 mg or matched placebo, study medication will be discontinued. Treatment will be provided in similar capsules format to be taken orally 1-2 times a day. Investigators, study personnel and participants will be blinded for drug assignment. Participants will be treated for 1 year.

5.2. HANDLING OF STUDY INTERVENTIONS

The drugs will be stored in the medication room in the Investigational Drug Service (IDS) Pharmacy. The primary location of the IDS pharmacy is The Emory Clinic Bldg. A, Suite 1200, 1365 Clifton Road, NE, Atlanta, Georgia 30322. This location will serve the satellite Emory IDS pharmacy used for this study, at the Executive Park campus. Access to the med room is limited to the IDS Pharmacists via a badge swipe. Accountability records are maintained for all investigational product (IP). A courier will deliver prescriptions to study location to be given to subjects or study staff will be able to pick up prescriptions.

5.3. CONCOMITANT INTERVENTION

5.3.1. ALLOWED INTERVENTIONS

Participants will continue to receive their usual care from their regular primary care physicians. In the event that during the trial period, a participant is required to be on a LTRA (Montelukast or other similar agents), the prescribing physician and the subject will be informed they might be receiving Montelukast to avoid any overlap. If an alternative treatment is prescribed that is safe to be used with Montelukast, then they can continue on the study medications. Participants who start on a LTRA (or a drug that potentially lead to contraindication for using LTRA) clinically will have their study medication discontinued but will continue to be in the study and have their subsequent visits and measures completed.

5.3.2. PROHIBITED INTERVENTIONS

Participation in another clinical trial or study is prohibited.

5.4. ADHERENCE ASSESSMENT

Participants will be asked to bring their study medication bottles to the study center at each visit. Medication compliance will be assessed using pill count during the follow up periods. We will define a compliance rate for a time period, t, as the ratio of: ((the used number of pill prescribed for the number of days t - number of pills remaining or unused for the time t)/ number of pills prescribed for time t) multiplied by 100.

6. STUDY PROCEDURES AND MEASURES

6.1. QUESTIONNAIRES, LIFESTYLE AND ANTHROPOMETRIC MEASURES

Study interviews will be conducted in English and include the following:

(1) Demographic, social, stress, physical activity using the Physical Activity Scale for the Elderly (PASE),[35,36] and medical history data, as well as a medication inventory will be collected. All participants are asked to bring all their prescribed medication bottles.

(2) Functional Activities Questionnaire (FAQ),[37] Functional Assessment Staging Tool (FAST),[38] and Instrumental activities of daily living (IADL) scale.[39]

(3) Weight and height (stadiometer to measure height with the subjects standing and balance beam scale to measure weight without shoes).

(4) Short Physical Performance Battery (SPPB): ability to stand with the feet side-by-side, semi-tandem, and tandem, time to walk 8 feet (measured twice), and time to rise from a chair and return to the seated position 5 times.[40]

(5) Additional questionnaires will be collected at various visits including The University of California, San Diego Brief Assessment of Capacity to Consent (UBACC),[41] NIH Toolbox Perceived Stress and Hostility,[42,43] Race and Ethnicity Scale (RES), and Everyday discrimination scale (EDS).[44]

6.2. BLOOD PRESSURE MEASUREMENT

Office blood pressure will be measured according to the American Heart Association guidelines[45]- sitting position, rested for 5 minutes, appropriate cuff size (covering 60% of upper arm length and 80% of arm circumference), correct cuff placement (1-2 inches above brachial pulse on bare arm). Measurement will be done manually using the bell of the stethoscope or using a validated and calibrated automatic machine. Blood pressure will be measured in both arms. The arm with the higher blood pressure will be used throughout the study. We will obtain 2 seated blood pressure measurements 5 minutes apart, followed by 2 standing readings at 1 and 3 minutes during each visit.

6.3. NEUROPSYCHOLOGICAL ASSESSMENT:

(i) *Clinical Dementia Rating (CDR)*: The CDR rates each of the six general domains (or boxes) involving memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care, and a global rating is then generated, ranging from 0-no impairment to 3-severe impairment. A study informant or study partner will be questioned either by phone or in person to assist with the CDR.

(ii) NIH Toolbox Cognition Battery (NIHTB-CB: (www.nihtoolbox.org))[46]: This is a computer-based test battery that reliably and validly assesses neurocognitive sub-domains in clinical trials, including working memory, episodic memory, processing speed, language, attention and executive function.[47] The NIHTB-CB has excellent psychometric properties with test-retest reliability up to 0.92, and correlates (r=0.78-0.90) with Gold Standard Fluid, Crystallized and Total cognitive composites measuring everyday executive functioning.[48-50] Parts of the NIH Toolbox that we selected include:

1) Flanker Inhibitory Control and Attention test assesses attention and executive function and involves the allocation of one's limited capacities to deal with an abundance of environmental stimuli.[51]

2) Picture Sequence Memory test, a measure of episodic memory assessing cognitive processes involved in the acquisition, storage and retrieval of new information.[52]

3) List Sorting Working Memory test assesses working memory.[47]

4) Picture Vocabulary test assesses language by measuring receptive vocabulary.[53]

5) Pattern Comparison Processing Speed test assesses processing speed, the amount of information that can be processed within a certain unit of time.[54]

6) Dimensional Change Card Sort Test, a test of executive function, will assess cognitive flexibility and the capacity to plan and organize.[51]

(iii) To assess additional cognitive domains/mood, we will use these tests, some of which are included in the National Alzheimer's Coordinating Center Uniform Data Set.[55,56]

1) Verbal Fluency will be tested using a List Generation test which require the participant to generate words beginning with a specific letter, and category fluency in which the participant generates words from a specified category (e.g., animals, fruits).[57]

2) Hopkins Verbal Learning Test will be used to assess memory domains.[58]

3) Digit Span Test (DST) is a brief task that assesses attention.[59,60]

4) Boston Naming Test assesses language by measuring ability of naming a visual confrontation drawing (15 items).[61,62]

5) Trail Making Test will be used as an additional measure of executive function.[63]

6) Center for Epidemiologic Studies Depression Scale (CESD),[64] consists of 20 items, each scored from 0 to 3 points and higher scores indicate greater depressive symptoms.

7) Sheehan Suicidality Tracking Scale (S-STS), a sensitive psychometric tool to prospectively monitor for treatment-emergent suicidal ideation and behaviors in AD clinical trials.[65,66]

8) Neuropsychiatric Inventory Questionnaire (NPI-Q), a concise assessment of behavioral changes in patients with AD or other dementias.[67-69]

9) Montreal Cognitive Assessment (MoCA), a brief screening test for cognitive impairment in older adults.[70,71]

(iv) Voice recording to assess speech changes related to cognitive function may be collected at one or more visits. These will include a recording of the cognitive tests, free speech, speech in response to questions, and speech in response to specific cognitive tasks such as counting, fluency and/or a picture description. All voice recording files will not contain personal identifiers or PHI. They will be saved under the subject deidentified study number.

6.4. CEREBROSPINAL FLUID (CSF) COLLECTION

Participant will have CSF acquired via lumbar puncture (LP). In some instances, subjects would have had an LP as part of clinical evaluations or other research studies. If we obtain samples from the prior LP (within 6 months of the baseline visit) and sufficient samples are available for the molecular analysis, then baseline LP will not be necessary. Otherwise an LP will be done at baseline. All CSF samples will be collected after at least 6-hour fast from the last meal. CSF will be collected using a 24-g Sprotte atraumatic spinal needles. This needle decreases the frequency of post LP headaches to < 1%.[72] All CSF collection is completed according to guidelines put forth in the "Biospecimens Best Practice Guidelines for the ADCs" published by the National Alzheimer's Coordinating Center (NACC) and available on their website. Approximately 30-45 ml of CSF will be collected using sterile polypropylene collection tubes. The samples will be immediately divided into aliquots and transferred for storage in a freezer for future assays.

6.5. BRAIN MRI PROTOCOLS

MRI protocols are performed in 50-60 minutes and will be conducted at the Emory Center for Systems Imaging (CSI) core. The MRI protocol includes:

(i) Structural MRI and WMH: High-resolution anatomical images will be acquired using a 3D-Fast Spoiled Gradient Recalled Echo (FSPGR) Sequence. WMH regions will be identified by a 3D T2 Fluid Attenuated Inversion Recovery (FLAIR) Fast Spin Echo sequence.

(ii) ASL-MRI: ASL images will be acquired using a custom 3D stack of interleaved spirals fast spin echo sequence and will be averaged in order to improve the signal-to-noise ratio.

(iii) Diffusion tensor imaging: DTI is highly sensitive to detect structural changes over a short time, less than 1 year, as compared to traditional MRI.[73]

(iv) Resting state functional MRI (rs-fMRI): Resting state fMRI will be used to assess "functional connectivity" between brain regions. Functional connectivity has a key role in important complex cognitive processes.[74] It focuses on spontaneous, rather than task-induced low frequency (<0.1 Hz) fluctuations in the blood oxygenation level-dependent (BOLD) signals.

6.6. VASCULAR MEASURES

Arterial stiffness and microvascular function: Pulse-wave velocity (PWV) measured between carotid and femoral arteries is a regional assessment of aortic stiffness and is the gold standard index of arterial stiffness.

Blood pressure and Pulse-wave analysis (PWA): A brachial BP will be measured twice while seated and after 1 and 3 minutes standing according to the AHA guidelines.[45] Radial pulse wave analysis (SphygmoCor®, Atcor Medical, Australia) will be acquired as described previously.[75-77]

6.7. LEUKOTRIENE INHIBITION ACTIVITY

Cysteinyl leukotrienes (LTE_4) and CysLT type-1 (CysLT1) receptor activity will be assessed via single blood or urine sampling at baseline, 6 and 12 month visits by a highly selective and sensitive Liquid Chromatography/Tandem Mass Spectrometry (LC/MS/MS) method described previously.[78,79] We will use this as a measure to assess the degree of blockade of CysLT type-1 (CysLT1) receptor activity.

6.8. BLOOD CHEMISTRIES AND BLOOD COUNT

Blood will be drawn at various visits. Please refer to **Table 1** for specific tests done at each visit.

6.9. BLOOD AND CSF BANKING

We will collect blood and CSF samples for future research. Vials containing blood samples, which will include serum, plasma and buffy coat as well as other blood products will be labeled with subject ID numbers, barcoded and stored at the cryogenic storage facility until time of processing. The label will include the study name, study visit number, contents of each collection vial, and the date of collection. The samples will be kept until the samples are exhausted. Future study results obtained from these samples may not be reported to subjects.

6.10. SCHEDULE OF EVALUATIONS

6.10.1. SCREENING

Individuals who express an interest will first participate in a screening process. During the remote (phone/virtual) or in-person screening visit, after informed consent has been obtained either on paper or electronically, we will collect demographic and medical information, and perform a series of tasks to determine subject safety and eligibility to participate in the study e.g. blood pressure checks, cognitive testing, lab testing. See Table 1 for detailed information on study procedures performed at screen visit.

Participants meeting eligibility criteria detailed in Section 4 (Selection and enrollment of participants) will be scheduled for the baseline visit.

6.10.2. ENROLLMENT, BASELINE, AND FOLLOW-UP

Once eligible, baseline evaluation will be completed. A clinical evaluation and LP will be done during the baseline visit, unless one was done earlier during screening. Biospecimens will be collected for inflammatory and endothelial markers. Once baseline data are collected, participants will be randomized into Montelukast or placebo. During the medication escalation period, participants will be monitored via follow-up phone calls every 2 weeks until max dose is achieved, or participant reports adverse events (see intervention for issues related to increased LFT). Participants will return for follow-up visits at 6 weeks post-randomization, and at 3, 6 and the final 12-month visit. Blood pressure, heart rate, weight, laboratory testing, adverse events (AE) or serious adverse events (SAE), pill count (to assess compliance), and use of non-study medications data will be collected for frequent monitoring. At least 1 follow-up phone call will also occur between 6 and 12 months. An optional modified phone/virtual visit will be completed as needed for any visit to collect data that can be reasonably collected by phone. This change is in response to the COVID-19 stay home orders. However, subjects will be given the option to continue doing portions of the visits virtually when normal business operations resume. All visits will have a +/- three-week window for subjects to reschedule as needed, except for the 6-week visit which will have a +/- one-week window. Study procedures and timeline are shown in **Table 1**.

7. SAFETY ASSESSMENTS

7.1. SPECIFICATION OF SAFETY PARAMETERS

(i) The following safety parameters are related to the use of Montelukast: The finding of an elevated ALT, AST, or bilirubin (> 3 x ULN) or other clinical evidence of liver disease such as jaundice, encephalopathy. Headache, stomach cramps, fever, nasal congestion, upper respiratory tract infection and throat irritation are less common side effects.

Other infrequent side effects of Montelukast include runny nose, diarrhea, dizziness, fatigue, joint or muscle pain, bronchitis, gastroenteritis, pancreatitis, rash, dental pain, and ear or skin disorders. Angioedema, eosinophilia, vasculitis, increased bleeding tendencies, seizures, altered behavior and suicidal thoughts are also rare but potential complications of Montelukast.

(ii) The following safety parameters are related to the conduct of the study procedures: Neuropsychological assessment may be accompanied by anxiety, frustration and overall fatigue. The attachment and removal of a blood pressure cuff, cuffs for venous occlusion, and ultrasound probe on the neck may cause mild discomfort. Brain imaging requires the participant to stay still and lie down for 50-70 minutes, which may cause boredom and minimal reversible back pain. Because of the closed space and noise, undergoing an MRI may be associated with anxiety or panic reactions. The vascular ultrasound is safe and only mildly uncomfortable due to discomfort in the arm when the cuff is inflated. We will use ultrasound to painlessly bounce sound beams off the carotid artery using a pencil-like sensor.

(iii) The following safety parameters are related to the LP procedure: The most common complication of a lumbar puncture is post-LP headache. We use a smaller 24-gauge Sprotte spinal needle. All subjects will be counseled on the signs and symptoms of post-LP headaches and given information on management (acetaminophen, caffeine, rest). Bacterial meningitis and a CSF leak are very rare complications of lumbar punctures. A blood patch is rarely needed to heal CSF leaks. All subjects will be instructed to promptly contact us if the headache persists beyond 3 days and if a blood patch is required, the cost of the patch will be covered by the funds supporting this project.

7.2. METHODS FOR ASSESSING AND RECORDING SAFETY PARAMETERS

During the study, any problem reported by the participants will be recorded in the participant's research record (adverse event log), along with the start and stop dates. The problem may be related to the research participation or the drug used in the study (drug reaction). All adverse events will be rated on the following characteristics:

(i) Serious (YES/NO): A serious adverse event (SAE) is defined using the Code of Federal Regulations Title 21 definition as any event that results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

(ii) Related to the research: All adverse events will be judged regarding their relationship to the research participation or the study drug as related, possibly related, probably related, unrelated, or unknown.

(iii) Severity: The severity of the AE will be rated on the following scale mild, moderate, severe, life-threatening, or death.

(iv) Anticipated or unanticipated: We use the Emory IRB definition of an unanticipated event as any event that is "unexpected, not described in the study documents, or if described before, it is now presenting with increased severity, duration, or frequency".

7.3. REPORTING ADVERSE EVENTS AND DEATH

All adverse events will be assessed for the need for prompt reporting. We follow the guidelines set forth by the Emory IRB for reporting AEs. Any event that fulfills the following criteria being unanticipated (as defined in section 7.2), probably or possibly related to study participation (drug effect or as a consequence of a study procedure), and involving risk for participants or others is considered an unanticipated problem and will be reported to the Emory IRB within 10 days. If an event could be explained by the underlying medical condition, it is not considered related and hence not reportable. Any SAE as defined in **section 7.2** that does not fit all the criteria of being an unanticipated problem will be reported during continuing review. Deaths of participants during the study will be promptly reported to the IRB if related to study participation and reported during continuing review if they are not related to study participation.

7.4. FOLLOW-UP FOR ADVERSE EVENTS

All AE/SAE will be recorded in the participant chart with start/stop date. The study physician may perform additional evaluations, unscheduled visits, phone communication, repeat blood testing, or refer to the emergency room or the participant healthcare provider for medical care if necessary. If the event results in intervention discontinuation (>5 months) but not study withdrawal, the participant will be followed as defined in the study. They will also be invited to perform the final visit evaluation including all study procedures planned for that visit if the participant has been in the study for more than 5 months post-baseline evaluation.

When a subject notifies the study team that they have symptoms suggestive of a treatment-emergent AE/SAE, the study physician will review the incident and determine if the subject is safe to continue in the study. The physician may discontinue the study medication immediately, elect to lower the dose of the study medication, ask subject to present to the study center for a safety evaluation, and/or monitor the subject's concern. The subject may continue in the study if on the lower dose of the study medication, they experience some resolution of symptoms. In those on 20 mg and 40 mg, the doses will be decreased to the next lower dose. In those on 10 mg of Montelukast, a trial of every other day 10 mg of Montelukast will be attempted prior to discontinuation.

7.5. INCIDENTAL FINDINGS

Incidental findings (lab testing, neuroimaging or vascular testing) identified during the conduct of the study that do not require immediate medical care will be reported to the subject with instructions to seek medical care from the participant's healthcare provider. Those with incidental findings requiring urgent care will be referred to an emergency room in a facility of their choosing.

8. INTERVENTION DISCONTINUATION AND STUDY WITHDRAWAL

A subject may choose to withdraw from the study for any reason. Also, the investigators may also request that a subject withdraw from the study or intervention be discontinued, for safety or other reasons. The criteria for intervention discontinuation or study withdrawal may include:

(1) The subject's request;

(2) Inability to participate due to relocation or other personal reasons;

(3) Adverse events that requires un-blinding or necessitate stopping the study drugs;

(4) Seizures;

(5) Persistent increase in elevated liver enzymes following study dose de-escalation or clinical or biochemical evidence of hepatic disease.

9. STATISTICAL CONSIDERATIONS

9.1. GENERAL DESIGN

The study is a 2-arm double-blinded RCT. The statistical analysis will follow the intention-to-treat approach. Intention-to-treat (ITT) and per-protocol analyses will be performed.

9.2. RANDOMIZATION

The study blinded biostatistician will provide oversight of randomization fidelity and blinding. Randomization will be stratified by **use of cholinesterase inhibitors or Memantine (yes vs no)** and by **cognitive group** (MCI vs early AD) using a computerized random number generator (SAS, V9.4). Only the pharmacy will have access to the randomization lists. As the pharmacist is notified that an individual subject is eligible for randomization, the pharmacist prepares the appropriate blinded study product. The pharmacist will enter the subject ID, date of product randomization, and the unique allocation sequence number on a web-based data form.

9.3. DATA ANALYSIS

Table 2 provides a list of main outcomes.

Table 2. Independent, main outcome and other variables to be used in the analyses	
Independent:	Group (Montelukast vs placebo)
Safety outcome:	GI symptoms (diarrhea, nausea, vomiting), anaphylaxis, elevated liver enzymes, PT/INR, behavioral changes, seizures, number of discontinuations from Montelukast, treatment-emergent AE/SAE, deaths
CSF outcomes:	CSF amyloid and tau, inflammatory proteins
Vascular outcomes:	PWV/PWA
Imaging outcomes:	Perfusion, hippocampal volume
Cognitive outcomes:	CDR, NIH Toolbox Cognition battery (NIHTB-CB)

Baseline characteristics including demographic, social and cognitive measures will be compared between the 2 groups to assess randomization fidelity. The list of the main variables is shown in Table 2. We will compare the change in our outcomes over the study period between the treatment and placebo arms using Mixed Models. For the dose response analysis, the dose vs cysLT-1 receptor activity will be plotted to explore the degree of cysteinyl leukotriene modulation at the various doses.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1. DATA COLLECTION FORMS

Data collected during interviews and exams will be documented on trial-specific data forms. Neuroimaging and ultrasound data will be saved in digital formats on a HIPAA-compliant server.

10.2. DATA MANAGEMENT

Once a subject is enrolled into the study, he/she will be assigned a unique identifier number and be referred to by initials and the study number only. Only research team members will have access to the files. Data will be entered on a web-based secure trial data system; the trial database will include for all variables an electronic data audit of data edits (who, when, and why). A data query report (including missing, out of range, and logic checks) will be generated by the trial statistician. The investigators will keep subjects' medical records private as far as the law allows. The IRB and officials of the sponsor/funding agency will have access to these records as needed within legal guidelines. If study results are published in journals or presented at meetings, we will not use the subjects' names.

10.3. QUALITY ASSURANCE

10.3.1. TRAINING

Research personnel will be trained by a program manager well versed in study procedures. All personnel involved in cognitive assessment will be trained and supervised by the study neuropsychologist. The process of training on data form completion, neuropsychological assessment and subject evaluation will be documented in a training log for each study personnel.

10.3.2. QUALITY CONTROL (QC)

To assess protocol compliance and quality of data collected, the PI along with another investigator will randomly and on intervals review data obtained. In addition, assessment of personnel competencies in obtaining data will be performed. Data will also be checked during QC data meetings and interval cumulative reports will be reviewed.

10.3.3. PROTOCOL DEVIATIONS

Every attempt will be exercised to maintain compliance with the approved study protocol. In the event when a deviation is noted, the Emory IRB will be notified as required by IRB Policies & Procedures only if the deviation affects the rights or welfare of subjects, the safety of subjects, the willingness of subjects to continue with study participation, or the integrity of the research data. The PI or designated personnel will conduct an investigation about the setting, reasons, and potential remedies that need to be instituted to rectify the deviation and prevent future similar instances.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1. INSTITUTIONAL REVIEW BOARD (IRB) REVIEW

This protocol and the informed consent document and any subsequent modifications will be submitted and reviewed by the Emory IRB.

11.2. CONSENTING PROCEDURE, INFORMED CONSENT FORMS, AND STUDY INFORMANTS

A signed consent form will be obtained from each participant or the participant's legally authorized representative. A single informed consent form will describe both the screening and study procedures. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant and this fact will be documented in the participant's study record.

During the consenting process, an assessment for decisional capacity to participate in clinical research will be performed. This is conducted by asking the subject a set of study-specific questions. A validated brief instrument for decisional capacity assessment will be administered:[41] The University of California, San Diego Brief Assessment of Capacity to Consent (UBACC) instrument is a 10-item questionnaire that asks the participant about key areas of the informed consent. A score greater than 14.5 correlates with a score of greater than 16 on the MacArthur Competency Assessment Tool for Clinical Research (MacCAT-CR).[41] MacCAT-CR is the most validated instrument in assessing decisional capacity in clinical research[80] and a score greater than 16 has been traditionally considered adequate in prior NIH studies.[81]

Participants who are unable to answer the capacity assessment questions correctly (UBACC score <14.5) may still qualify for the study but will need to have a surrogate and a study informant. The definition of the surrogate will be consistent with the intent of the Common Rule (45 CFR 46, Subpart A). The following are, in order, possible surrogates:

(1) The person's agent designated by an advance health care directive.

(2) The conservator or guardian of the person having the authority to make healthcare decisions for the person.

(3) The spouse of the person.

(4) The domestic partner of the person as defined in Section 297 of the Family Code.

(5) An adult son or daughter of the person.

(6) A custodial parent of the person.

(7) Any adult brother or sister of the person.

(8) Any adult grandchild of the person.

(9) An available adult relative with the closest degree of kinship to the person.

When there are two or more available persons who are in different orders of priority pursuant to subdivision (c), refusal to consent by a person who is a higher priority surrogate shall not be superseded by the consent of a person who is a lower priority surrogate. That surrogate will need to consent to the study. If either party refuses, we do not enroll the subject. To ensure both the participant and the proxy understand the study protocol, we will ask subjects or legal next of kin to explain in their own words the nature of the study and the procedures involved.

The proxy will be considered the study informant if there is contact at least once a month. In some instances, such as the lack of adequate contact by the surrogate or the surrogate's inability to complete the tasks of the study informant, the study informant may be a different individual as long as he/she is willing to provide information about the participant and have contact with the participant for at least once a month (in person or telephone). The study informant will sign the study informed consent. If they are not available in person, the study staff will contact the informant to obtain needed information about the subject cognitive symptoms. In that case, a verbal consent will be obtained.

11.3. PARTICIPANT CONFIDENTIALITY

Only the investigators will have access to information about study subjects. A subject's primary care physician will only be notified if the subject agrees. To maintain confidentiality, subject data will be referenced by number and stored in locked computer files and cabinets. Identifying information about a subject will not be used during the discussion, presentation, or publication of any research data. Only research team members will have access to the files. Data recorded and stored on the computer will be backed up to a disc and stored with the paper files. Participants will not be given any results of the research procedures unless there is a medical necessity. This will be clearly stated in the informed consent process.

11.4. PARTICIPANT COMPENSATION

Subjects will be compensated with gift cards for their effort and time at the following schedule:

- Screen Visit: $25
- Baseline Visits: $100 (for visit + MRI) + $100 (for lumbar puncture procedure)
- 6-week and 3-month Follow Up Visits: $25
- 6 Month Follow Up Visit: $50 (cognitive testing, blood draw)
- 12 Month Follow Up Visit: $100 (for visit + MRI) + $100 (for lumbar puncture procedure)
- Return Visit for blood redraw $25 and LP $100 (as needed)Transportation: Up to $30 for gas reimbursement and up to $50 for taxi or shuttle service to the study site

11.5. STUDY DISCONTINUATION

The study may be discontinued at any time by the investigators, the Emory IRB, the OHRP or other government agencies as part of their duties to ensure that research participants are protected.

12. PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures of Emory.

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