Cover Page

Protocol Title:
Anti-viral treatment in Mild Cognitive Impairment
IRB Protocol Number:8089

NCT number 04710030

First IRB Approval:
01/08/2021
Version Date:
11/24/2023

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Anti viral treatment in Mild Cognitive Impairment

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Protocol Number:
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First Approval:
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Research Area:
Brain Aging & Mental Health

Expiration Date:
11/22/2024

Division:
Geriatric Psychiatry

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Research Chief:
Davangere Devanand, MD

Cover Sheet

Choose ONE option from the following that is applicable to your study
If you are creating a new protocol, select "I am submitting a new protocol." As 5 Year Renewals are no longer required, this option remains for historical purposes.
I am submitting an annual continuation with modifications

Department & Unaffiliated Personnel

Department

What Department does the PI belong to?
Geriatric Psychiatry
Within the department, what Center or group are you affiliated with, if any?
Memory Disorders Clinic (MDC)

Unaffiliated Personnel

List investigators, if any, who will be participating in this protocol but are not affiliated with New York State Psychiatric Institute or Columbia University. Provide: Full Name, Degrees and Affiliation.
Memory Disorders Clinic (MDC)

Amendment

Describe the change(s) being made
We have updated our Informed Consent Form document based on the language recommended in the MRI Principal Investigator Update training session held on August 15, 2023. We have uploaded the PowerPoint slide regarding ICF language created by Rachel Marsh, which includes the template wording that was incorporated into our ICF. We are increasing the enrollment sample size from 50 to 56. Additionally, we removed the checkboxes from the "DPD Eligibility Confirmation" form and simplified the language used on this form. PI Dr. Devanand will use this form to certify that all patients who are active in the protocol met the Inclusion Criteria, which were updated as a part of the Protocol Restart package (approved 9/18/2023), at screen. We also removed the checkboxes and signature line for the Program Manager on the "Full Inclusion/Exclusion Criteria" form as there is no current Clinical Program Manager, nor do we foresee hiring a Clinical Program Manager in the future.
Provide the rationale for the change(s)
The template wording in the "MRI Updates Consent Form Guidance" upload was recommended by Director of Operations at the NYSPI MRI suite, Matthew Riddle, during the MRI Principal Investigator Update training session. Under "Sample Subject Population" in the PSF, we had projected 50 enrolled patients and 50 completers to Under "Sample Subject Population" we had projected 50 enrolled patients and 50 completers to accomplish study goals. These numbers do not account for dropouts. We are defining completers as patients who complete Wk 0 (Baseline) procedures and at least one in-person follow-up visit (i.e., Wk 12). We are employing intent-to-treat (ITT) analyses (linear mixed model analyses) as specified in the PSF from its inception in 01/2021. To account for dropouts and the ITT analytic plan, we are increasing the projected number of enrolled patients from 50 to 56; 56 enrolled (randomized) patients will allow us to account for dropouts within the ITT analytic framework. This number of 56 will allow us to include 4 patients who completed screening procedures but could not proceed with randomization due to the institution-wide research pause. We plan to enroll/randomize these patients as soon as possible. As a result of this modification, we expect to have 50 completers among the 56 enrolled/randomized patients. This has been reflected in the "Sample Subject Population" section of the PSF. Updates were made to "DPD Eligibility Confirmation" and "Full Inclusion/Exclusion Criteria" as per Dr. Devanand's guidance. The rationale for these changes is detailed in the response to "Describe the changes being made".
Comment on the extent to which the proposed change(s) alter or affect risks/benefits to subjects
This change will not alter or affect the risks/benefits to subjects.
Comment on if the proposed change(s) require a modification to the Consent Form (CF)
Yes, the Consent Form has been modified using the template language drafted by Rachel Marsh. We have uploaded bolded and un-bolded (to be stamped) versions of the updated Consent Form dated 9/29/2023. These changes are located under "MRI (Magnetic Resonance Imaging) Brain Scan" and "Risks and Inconveniences" (subsection: MRI Scan).

Application for Continuation of Research

Status

Current Status of Study:

Subject enrollment is ongoing.

Summary of Experiences to Date

Please provide a summary of scientific progress of the study and the experience of research participants, to date. This requirement is designed to allow for the investigator and the IRB to reassess the study's risks and benefits in terms of developments in the field, changing practice patterns, and new IRB policies and procedures.

The goals of this project are to evaluate valacyclovir, a repurposed generic antiviral drug, as a treatment for mild cognitive impairment (MCI). VALMCI is a Phase II, randomized, double-blind, placebo-controlled, 52- week treatment trial of 56 patients (28 valacyclovir, 28 placebo) with amnestic MCI (eMCI and lMCI) who are HSV seropositive and AD-biomarker positive. Research participants are continuing along the timeline of the protocol. So far, 24 participants have completed protocol participation (this is a 52-week protocol and our first randomized participant completed baseline measures on 19May2021). The infrequent side effects of the medication, availability of the research team, and comprehensive testing continue to bolster our enrollment and retention rates. Only 3 participants have withdrawn consent, terminating treatment before 52 weeks. One participant has been withdrawn from the protocol due to prescription of a concomitant medication (valacyclovir). Throughout the duration of the protocol to date, 115 subjects consented to blood draw for HSV antibodies; of these 115 subjects, 97 tested positive for HSV antibodies while 18 tested negative for HSV antibodies and screen failed. Of the 97 HSV positive subjects, 81 patients underwent 18F-Florbetapir PET imaging. Of the 81 subjects who completed 18-F Florbetapir PET imaging, 61 were determined to be AD-biomarker positive while 20 were AD-biomarker negative and screen failed. Of the 61 AD-biomarker positive subjects, 49 agreed to be randomized into the protocol. There are no new developments in the field that impact on the science of the risk/benefit balance of this protocol.

Funding

Have there been any changes in funding status since the prior approval?

No

Have the principal investigator and other investigators made all required disclosures of financial interest in the study sponsor/product?

Yes

Summary

Have there been any study findings, recent literature, or untoward events occuring here or at other sites in the past year which might affect the analysis of the safety, risks or benefits of study participation?

Yes

Please indicate how the new information affects the study's risk/benefit analysis and comment on whether consent form changes are necessary.

Yes, due the NYSPI research pause and safety review, research procedures including clinic visits, blood draws, MRIs, and PET scans were not completed between July 18, 2023 and September 24, 2023. On June 27, Dr. Devanand and the #8089 research team received the IRB Continuation Review, which indicated that only prescription of study medication could continue during the institutional pause. However, six patients

completed study procedures between 6/27/23 and 7/18/23. No adverse events were reported by patients during these procedures; however, the completed research procedures were reported to the IRB as a Protocol Deviation on 7/26/2023. A corrective action plan has since been established and the Protocol Deviation has been resolved by the IRB. This Protocol Deviation was considered a serious noncompliance issue; however, the IRB did not indicate any change to the safety or risk/benefit analysis of study participation.

Have there been any serious adverse events (serious and/or unanticipated problems involving risks to subjects or others at this site which occured in the past year)?

Yes

Please describe them and indicate resultant protocol modifications made.

Yes, since the 2022 ACAR was submitted, there has been one Serious Adverse Event. ID 435: Subject 435 is a 52-year-old Caucasian woman, diagnosed with early mild cognitive impairment. The subject was randomized on 10/13/2022. She titrated up to 4 grams of valacyclovir vs. placebo per protocol. The SAE occurred on 3/24/2023, however was reported to the research coordinator by the subject on 04/25/2023 during a routine clinic visit. Patient started to feel a tightness in her chest on 3/24/2023 while on a cruise through South America. As symptoms worsened, she was admitted into the ICU on 3/26/2023 and received diagnoses of pneumonia, bronchitis, and a UTI infection. Patient was discharged from the ICU on 3/28/2023. Patient's vomiting, unmanageable phlegm and difficulty breathing ceased on 3/30/2023. Patient's only remaining symptoms of coughing and wheezing fully resolved by 4/14/2023. Study medication was interrupted for 4 days and was resumed after she was discharged from the ICU. This SAE was determined to be unrelated to the study medication. Protocol modifications were not necessitated by this SAE.

Have all study staff with a significant role in the design or implementation of the human subject components of this study received required training in human research subject protections?

Yes

Is the study covered by a certificate of confidentiality?

Yes

Certificate expiration date (mm/dd/yyyy)

12/31/2023

Overall Progress

Approved sample size

50 (plan to increase enrollment to 56 as per note below)

Total number of participants enrolled to date

49

Number of participants who have completed the study to date

24

Have there been any significant deviations from the anticipated study recruitment, retention or completion estimates?

No

Comments / additional information

Sample Demographics

Select the # of samples applicable

Poor

Specify population
White (non-Hispanic or Latin)
Total number of participants enrolled from this population to date
23
Specify population #2
Black/ African American
Total number of participants enrolled from this population to date
13
Specify population #3
Hispanic/ Latino
Total number of participants enrolled from this population to date
8
Specify population #4
Other/Mixed
Total number of participants enrolled from this population to date
5
Gender, Racial and Ethnic Breakdown
Out of the 49 randomized participants, 23 (47%) identify as white and non-Hispanic. Of the 23 white and non-Hispanic participants, 13 are men and 10 are women. Out of the 49 randomized participants, 13 identify as Black or African American. Of the 13 Black/African American participants, 3 are men and 10 are women. Out of the 49 randomized patients, 8 identify as being of Hispanic or Latino/a origin. Of the 8 Hispanic/Latino participants, 3 are men and 5 are women. Out of the 49 randomized participants, 5 identify as “Other” or “Mixed Race”. This group includes 3 men and 2 women.

Summary of Current Year's Enrollment and Drop-out

Number of participants who signed consent in the past year
59
Number of participants currently enrolled
49
Did the investigator withdraw participants from the study?
Yes
Circumstances of withdrawal:
Yes, Subject ID 557 was withdrawn from the protocol by the PI. ID 557 was prescribed Valacyclovir for a HSV-2 infection; concomitant open treatment with Valacyclovir is not permitted given that participants in this trial are assigned to Valacyclovir v Placebo.
Did participants decide to discontinue study involvement?
Yes
Circumstances of discontinuation:
Subject ID 413 withdrew consent at Week 50 due to unwillingness to make time commitments to the protocol. Subject ID 454 was lost-to-follow-up after Week 0 procedures were completed. Subject ID 548 withdrew consent at Week 4.

Procedures

To create the protocol summary form, first indicate if this research will include any of the following procedures

✓ Collection of Biological Specimens
✓ MRI
✓ Neuropsychological Evaluation
✓ Off-label Use of Drug or Device
✓ PET/SPECT Scan
✓ Psychiatric Assessment
✓ Studies of DNA
✓ Use of Investigational Drug or Device
✓ Use of Placebo or Sham Treatment

Population

Indicate which of the following populations will be included in this research

✓ Adults who may have impaired decision-making ability
✓ Adults over 50

New York State
Psychiatric Institute
Institutional Review Board
PRISM 2022

Protocol Summary Form

Instructions:

The new Protocol Summary Form is now included in this Word template. You will begin a new protocol by completing all sections which pertain to your study. Not all sections are required. If a section is not applicable to your study, place "N/A" in the section area.

If you are submitting an Amendment or Continuation, you will need to obtain a copy of the most recent approved PSF. This will be found in the list of forms submitted under the protocol selected. Once you have downloaded the PSF, you can convert the PDF to Word document using this link https://www.adobe.com/acrobat/online/pdf-to-word.html

After converting the PSF, you can copy the information to the new PSF Word template and make any changes to the PSF as necessary for your Amendment or Continuation. From here, follow the instructions provided for creating the appropriate form.

Research Support / Funding

This section is to describe the funding sources for your protocol.

If an internal account is to be used, please describe. **The internal account is ☒ RFMH** ☐ CU

If the project is using, or planning to use, external funding, provide the details for each external funding source.

Principal Investigator on grant/contract	**Dr. Devanand Davangere, M.D.**
Status of Grant (select one)	**is currently funded** application is in pending review or a funding decision is in preparation
Source of Funding (select one)	Federal / Industry / **Foundation** / Other (specify)
Institute / Agency	**Alzheimer's Association**
Grant Name	**Anti-Viral Treatment in Mild Cognitive Impairment #8089**
Grant Number	**R01AG055422**
Sponsor	**Alzheimer's Association**
Is this research initiated by the investigator?	**Yes.**
Site description (select one)	**Single Site** Multicenter (NYSPI is the lead site) Multicenter (NYSPI is a participating site) Multicenter (NYSPI is not a participating site)
Business Office (select one)	**RFMH** / CU / Other (specify)
If the grant/contract includes a subcontract, please describe. (To / From, Name of institution(s). Be sure to specify To or From)	**N/A.**

Study Location

Indicate if the research is/will be conducted at any of the following:

☒ NYSPI Facilities ☐ Washington Heights Community Service ☐ Other Columbia University Medical Center

This Protocol describes research conducted by the PI at other facilities/locations:

☐ Office Of Mental Health Facilities

☐ Binghamton Psychiatric Center	☐ Bronx Children's Psychiatric Center
☐ Bronx Psychiatric Center	☐ Brooklyn children's Psychiatric Center
☐ Buffalo Psychiatric Center	☐ Capital District Psychiatric Center
☐ Central New York Psychiatric Center	☐ Creedmoor Psychiatric Center
☐ Elmira Psychiatric Center	☐ Greater Binghamton Health Center
☐ Hudson River Psychiatric Center	☐ Hutchings Psychiatric Center
☐ Kingsboro Psychiatric Center	☐ Kirby Forensic Psychiatric Center
☐ Manhattan Psychiatric Center	☐ Middletown Psychiatric Center
☐ Mid-Hudson Psychiatric Center	☐ Mohawk Valley Psychiatric Center
☐ Nathan S. Kline Institute	☐ Pilgrim Psychiatric Center
☐ Queens Children's Psychiatric Center	☐ Rochester Psychiatric Center
☐ Rockland Children's Psyciatric Center	☐ Rockland Psychiatric Center
☐ Sagamore Children's Pyschiatric Center	☐ St. Lawrence Psychiatric Center
☐ South Beach Psychiatric Center	☐ Western NY Children's Psychiatric Center

Or type in location(s)..

Click or tap here to enter text.

☐ Hospitals, clinics and other healthcare facilities

☐ Bridge Plaza Medical Center

☐ Harlem Hospital

☐ St. Luke's-Roosevelt Hospital Center

☐ Mount Sinai Medical Center

☐ Weill Cornell Medical Center

Or type in location(s)..

Click or tap here to enter text.

☐ Schools/Educational Institutions

Type in location(s)..

Click or tap here to enter text.

☐ Prison System(includes Parole)

Type in location(s)..

Click or tap here to enter text.

☐ International Sites

Type in location(s)..

Click or tap here to enter text.

☐ Other Facilities

Type in location(s)..

Click or tap here to enter text.

☐ Community Sources

Type in location(s)..

Click or tap here to enter text.

Lay Summary of Proposed Research

This section is intended to provide a basic overview of the study including a description of its purpose, study procedures, and subject population. The summary should provide a concise overview of the study for non-scientific and scientific members of the IRB. Please avoid medical or technical terminology. In general, the abstract of a grant does not provide a suitable lay summary.

We will conduct a Phase II, placebo-controlled, 52-week trial using oral valacyclovir 4 g/day in 56 HSV-seropositive, AD biomarker-positive, amnestic mild cognitive impairment (MCI) patients (eMCI and lMCI).

The trial will directly address the long-standing viral etiology hypothesis of Alzheimer's disease (AD) which posits that viruses, particularly the very common herpes simplex virus-1 (HSV1) and HSV2, may be etiologic or contribute to the pathology of AD. This trial will intervene at an earlier stage (MCI). We will compare the repurposed drug valacyclovir (n=28) to placebo (n=28) in patients with amnestic MCI (eMCI or lMCI) in a randomized, double-blind, two-arm parallel group 52-week pilot trial. Our Phase II trial will be the first antiviral drug trial conducted in MCI.

Early MCI (eMCI) is a form a Mild Cognitive Impairment as is Late MCI (lMCI). EMCI subjects represent individuals with milder degrees of cognitive impairment than the lMCI subjects. Both eMCI and lMCI are subtypes of Amnestic MCI. The difference is defined by patient performance on specific cognitive tests with classification determined by cognitive test scores categorized by number of years of education.

Patients treated with valacyclovir are hypothesized to show less amyloid accumulation than patients on placebo, using 18F-Florbetapir PET imaging (screen to 52 weeks). Patients treated with valacyclovir are also hypothesized to show a smaller decline than patients on placebo on the PACC cognitive composite score (0 to 52 weeks). Lastly, patients on valacyclovir are hypothesized to show smaller decline than patients on placebo, on the ADCS-ADL-PI (functional measure; 0 to 52 weeks). As exploratory hypotheses, we will explore apolipoprotein E e4 genotype as a moderator, and changes in global clinical status (CDR sum of boxes), viral antibodies and proteomic assays, AD signature of MRI regional and whole brain cortical thinning, and plasma total tau, tau epitopes, and neurofilament light (Nfl) protein markers for neurodegeneration.

Valacyclovir, a pro-drug of acyclovir, is a generic anti-viral drug. Acyclovir is converted by HSV viral thymidine kinase into monophosphate and triphosphate forms that inhibit DNA polymerase and lead to HSV chain termination. Therefore, valacyclovir leads to death of infected cells but not non-infected cells and has efficacy against several herpes viruses.

Valacyclovir may be both symptomatic and disease-modifying because chronic use leads to prolonged HSV suppression in patients with HSV infection. Valacyclovir antiviral treatment showed equivocal results in two placebo-controlled studies in multiple sclerosis. A pilot, valacyclovir versus placebo trial in schizophrenia showed significant improvement in three memory measures from the Penn battery (Prasad 2013). There are no published, placebo-controlled antiviral treatment trials in MCI or AD (Devanand 2018). We are, in parallel and without any overlap of participants, conducting such a trial, R01AG055422 IRB# 7537, comparing oral valacyclovir 4 g daily to placebo in 130 patients (75 patients recruited to date) with mild AD followed for 78 weeks. Click or tap here to enter text.

Background, Significance, and Rationale

In this section, provide a brief summary of the status quo of the relevant work field and how the proposed study will advance knowledge. Specifically, identify the gaps in knowledge that your project is intended to fill. If no gaps exist that are obviously and directly related to your project, explain how your proposed research will contribute to the overall understanding of your field. Describe potential impacts of your project within your field of study and in a broader context. Provide a critical evaluation of existing knowledge. The literature review does not have to be exhaustive.

Background, Significance and Rationale: The viral hypothesis of Alzheimer's disease (AD) posits that viruses in the brain, specifically herpes simplex virus-1 (HSV1) and to a much lesser extent herpes simplex virus-2 (HSV2), may be etiologic or contribute to AD pathology. This trial will intervene at an earlier stage (MCI). HSV has been implicated for several reasons. HSV1 and HSV2 can trigger amyloid aggregation and their DNA is common in plaques.

Anti-HSV drugs reduce Aβ and P-tau accumulation in brains of mice infected with HSV1, and HSV1 reactivation is associated with tau hyperphosphorylation. There is a strong association between HSV1 and amyloid plaques in AD brains but not normal brains. After initial oral infection, HSV1 becomes latent in the trigeminal ganglion and can enter the brain via retrograde axonal transport. Recurrent reactivation with newly produced HSV viral particles, 'drop by drop,' can damage neurons and lead to neurodegeneration and AD pathology. Cell-to-cell passage of microRNAs of HSV is supported by amino acid homology between human p-tau and VP22, a key target for phosphorylation by HSV serine/threonine-protein kinase UL13, and there is exosomic secretion of HSV- 1-infected cells' L-particles. Therefore, reactivated HSV-1 may underlie intracerebral propagation of tau in brain. HSV can use a second mechanism to enter the brain.

Dendritic nerve terminals of olfactory receptor neurons are directly exposed, and macromolecules can enter olfactory receptor neurons and be transported trans-synaptically. Murid Herpesvirus-4 (MuHV-4), which like Epstein Barr Virus and Kaposi's Sarcoma- associated Herpes virus persists in memory B cells, can enter new hosts directly via olfactory neurons, and infect myeloid cells to spread.

Valacyclovir, a pro-drug of acyclovir, is the most widely used generic antiviral drug with over 15 years of worldwide use. It is approved for the treatment of HSV1, HSV2, varicella zoster (shingles), and chickenpox. No other available antiviral drug, e.g., acyclovir (intravenous), famciclovir and ganciclovir, has been shown to be superior to valacyclovir in the treatment of HSV1 and HSV2.

Recommended dose of oral valacyclovir for peripheral acute HSV infections is 1 to 3 g daily, and bioavailability is 54%. For long-term HSV suppression, the dose is 1 g daily. In patients with HIV infection and clinical AIDS, valacyclovir 8 g/day was associated with serious adverse events in 10% of patients including GI disturbances and headache, and thrombotic microangiopathy in a few cases. The difficulty in obtaining efficacy for any drug in AD or MCI has led us to target a dose of valacyclovir 4 g daily; 3 g is the upper end of approved doses for peripheral HSV infection and was effective in the schizophrenia pilot trial. Doses of 6-8 g daily are tolerated in healthy young adults but are toxic in patients with HIV. These high doses increase the risk of CNS toxicity including hallucinations and tremor, particularly in older adults with renal insufficiency. Therefore, for older adults with amnestic MCI, we have chosen the dose range of 4 g daily (valacyclovir will begin at 2 g daily (1 g twice daily) and then increase by 1 g/d every 2 weeks until 4 g/d (2 g twice daily) or the maximum tolerated dose that is then kept constant) this provides an acceptable tradeoff between the likelihood of therapeutic efficacy and risk of toxicity.

Based on our experience to date in the conduct of NYSPI protocol #7537; HSV1/HSV2 seropositivity rate is estimated to be 60-65%. Of the 76 patients we anticipate screening in one year's duration, we anticipate 52 patients to be HSV seropositive and recruiting 50 of these 52 eligible patients. Valacyclovir does not have any major drug-drug/drug-food interactions. The proposed

trial is appealing because it involves a novel, unique, understandable mechanism, uses oral capsules rather than I.V. medications, and valacyclovir is very safe.

Significance and Innovation: Antiviral treatment in AD-biomarker positive amnestic MCI (eMCI or lMCI) has not yet been studied in a clinical trial. This is the first clinical trial investigating the use of antiviral treatment in MCI.

The antiviral drug valacyclovir has been tested in multiple sclerosis (MS) with initially positive and then equivocal results. MS lesion size and disability were the outcome measures; cognition was not assessed.

In a randomized, double-blind, placebo-controlled, 18-week trial in 24 patients with schizophrenia with positive HSV1 titers, valacyclovir 3 g/day was superior to placebo with effect sizes of 0.79, 0.97 and 1.14 for tests of working memory, verbal memory, and visual object memory, respectively, from the computerized Penn battery. Subjective cognitive improvement of at least 30% sustained for 12 months was reported in 43 of 61 patients with chronic fatigue syndrome who received valganciclovir, a drug closely related to valacyclovir that is used to treat CMV. Valacyclovir also improves cognition in herpes simplex encephalitis (HSE).

A valacyclovir open treatment trial to examine biomarkers in 24 patients with AD is ongoing (clinicaltrials.gov NCT02997982; PI Lovheim).

VALAD trial: R01AG055422, Devanand PI, at Columbia with NYU (site PI Thomas Wisnewski) as a second site is also ongoing. Targeted N=130 patients with mild AD, MMSE 18-28, randomized to valacyclovir 4 g daily or placebo for 18 months (NCT03282916). Outcome measures: cognitive (ADAS- Cog) and function (ADCS ADL), and biomarkers: amyloid (18F-Florbetapir) and tau (MK-6240) PET imaging. MRI and ApoE genotype are assessed; CSF in subsample; plasma biomarkers not assessed. We have enrolled 80 patients to date and expect to complete recruitment by end-2021. The trial lasts 18 months for each patient; readout is by end-2022.

Valacyclovir is a pro-drug of acyclovir that is converted by viral thymidine kinase into its monophosphate (acyclo-GMP) and triphosphate (acyclo-GTP) forms. Acyclo-GTP is a potent inhibitor of viral DNA polymerase with 100 times higher affinity to viral than cellular polymerase. Viral enzymes cannot remove acyclo-GTP from the chain, which results in inhibition of further DNA polymerase activity and consequent chain termination. Its monophosphate form, acyclo-GMP, also incorporates into viral DNA, leading to chain termination. Therefore, valacyclovir leads to death of infected cells but it does not affect the DNA of non-infected cells; hence its side effect profile is benign. In patients with clinical HSV1 and HSV2 infection, and possibly AD or MCI, valacyclovir may be both symptomatic and disease-modifying because chronic use leads to prolonged HSV1 suppression.

Innovation: Our Phase II trial using valacyclovir 4 g daily versus placebo in patients with amnestic MCI with HSV1 and/or HSV2 seropositivity and AD biomarker positivity will be the first antiviral drug trial conducted in MCI. This will be the first study in MCI of anti-viral treatment effects on changes in PET amyloid imaging indices, cognition and function, with ancillary measures of MRI cortical thinning and plasma biomarkers of total tau, p-tau epitopes and neurofilament light (Nfl). The moderating effect of apoE e4 genotype will also be assessed. Long-term antiviral treatment with valacyclovir is first-in-class for patients with MCI.

Rationale and Implications of the Project: Finding the causes and treatments for AD and MCI are important public health goals. If the study goals are achieved it will have major implications for improving quality of life and reducing disability and healthcare costs in this growing demographic.

In an editorial, 31 senior scientists and clinicians pointed out that the scientific evidence strongly suggests that microbes may be a major cause of dementia, including AD. The review identified HSV1 as the most likely culprit, and suggested an antiviral treatment trial to potentially slow or arrest disease progression in MCI and AD. Our innovative proposal to conduct the first-ever

anti-viral drug treatment trial in MCI addresses this issue directly, but we recognize that HSV or other infectious agents are unlikely to be the sole cause of AD.

Specific Aims and Hypotheses

Concisely state the objectives of the study and the hypothesis or primary research question(s) being examined. There should be one hypothesis for every major study procedure or intervention. For pilot studies, it is important not to overstate the study's objectives. If there are no study hypotheses, describe broad study goals/aims.

Objective: To intervene at an earlier stage, we propose a Phase II placebo-controlled, 52-week trial using oral valacyclovir 4 g/day in **56** HSV-seropositive, AD biomarker-positive, amnestic MCI patients (eMCI and lMCI)

Aim 1: Compare accumulation of amyloid (18F-Florbetapir PET) on valacyclovir to placebo.

Hypothesis 1: Patients on valacyclovir will show less accumulation of amyloid than patients on placebo (18F- Florbetapir PET, 0 to 52 weeks).

Aim 2: Compare change in PACC cognitive composite score on valacyclovir to placebo.

Hypothesis 2: Patients on valacyclovir will show smaller decline than patients on placebo on the PACC cognitive composite score (0 to 52 weeks).

Aim 3: Compare change in ADCS-ADL-PI on valacyclovir to placebo.

Hypothesis 3: Patients on valacyclovir will show smaller decline than patients on placebo on the ADCS- ADL-PI (function measure; 0 to 52 weeks).

Exploratory Hypotheses: We will explore apolipoprotein E e4 genotype as a moderator, and changes in global clinical status (CDR sum of boxes), viral antibodies and proteomic assays, AD signature of MRI regional and whole brain cortical thinning, and plasma total tau, p-tau epitopes and neurofilament light (Nfl) protein markers for neurodegeneration.

Description of Subject Population

In this section, you are to describe each subject population of the study. The demographics of the population should reflect the gender and ethnic distribution of each population being studied. Enter each subject population's sample size, Gender, Racial, and Ethnic breakdown, and finally, describe each subject population.

We plan to enroll/randomize 56 participants. Of the 56 enrolled participants, we anticipate that 50 participants will "complete" the study, defined as completing Week 0 (Baseline) procedures and at least one additional follow-up visit, i.e., Week 12.

All 56 patients that we plan to enroll will need to meet criteria for diagnosis of amnestic MCI (eMCI and lMCI by ADNI criteria), HSV-seropositivity (HSV1 or HSV2, as specified in the Inclusion Criteria), and AD biomarker-positivity (positive 18F-Florabetapir Amyloid PET Scan or previous AD biomarker positive CSF – with low Aβ42 and high tau/p-tau). Either gender will be included.

The majority of older adults have had the HSV infection during their lifetimes with persisting serum antibodies to HSV1 or HSV2. The prevalence of serum antibodies to HSV1 or HSV2 leads us to believe that the demographic breakdown of subjects with both MCI and HSV will not significantly differ from the breakdown of all subjects with a diagnosis of MCI.

Both English and Spanish speaking subjects will be enrolled.

The total recruitment numbers for NYSPI/Columbia are 50 completers required to accomplish study aims.

Sample Subject Population:

Subject Population	Number of completers required to accomplish study aims	Projected number of subjects who will be enrolled to obtain required number of completers	Age range of subject population
AD-biomarker positive adults (male and female), diagnosed with amnestic MCI (eMCI or lMCI) who test positive for serum antibodies to Herpes Simplex Virus (HSV1) or Herpes Simplex Virus (HSV2).	50 AD-biomarker positive adults with amnestic MCI (eMCI or lMCI) who test positive for serum antibodies to HSV1 or HSV2.	56 AD-biomarker positive adults with amnestic MCI (eMCI or lMCI) who test positive for serum antibodies to HSV1 or HSV2.	50-95.

Gender, Racial, and Ethnic Breakdown:

No minority group is excluded from research participation. Based on our current clinic distributions at NYSPI, 65% are expected to be Non-Hispanic White, 15% Hispanic, 15% African American, and 5% Asian. This is the expected representation in the proposed study. Based on our experience in our clinics, women will constitute 60% and men will constitute 40% of subjects.

Suicide Risk Management Plan

This section will include all information regarding the Suicide Risk Management Plan.

NEW YORK STATE OF OPPORTUNITY. | New York State Psychiatric Institute
INSTITUTIONAL REVIEW BOARD

Always ask questions 1 and 2.	Past Month
1) Have you wished you were dead or wished you could go to sleep and not wake up?	
2) Have you actually had any thoughts about killing yourself?	
If **YES** to 2, ask questions 3, 4, 5 and 6. If **NO** to 2, skip to question 6.	
3) Have you been thinking about how you might do this?	
4) Have you had these thoughts and had some intention of acting on them?	High Risk
5) Have you started to work out or worked out the details of how to kill yourself? Did you intend to carry out this plan?	High Risk
Always Ask Question 6	Life-time / Past 3 Months
6) Have you done anything, started to do anything, or prepared to do anything to end your life? *Examples*: Collected pills, obtained a gun, gave away valuables, wrote a will or suicide note, held a gun but changed your mind, cut yourself, tried to hang yourself, etc.	High Risk

988 SUICIDE & CRISIS LIFELINE

Any YES indicates that someone should seek behavioral healthcare.
However, if the answer to 4, 5 or 6 is YES, get immediate help: Call or text 988, call 911 or go to the emergency room. STAY WITH THEM until they can be evaluated.

Download Columbia Protocol app

ANTI-VIRAL THERAPY IN MILD COGNITIVE IMPAIRMENT

Patient ID: Patient Initials: Date: Rater Initials:

Intervals: Screen, Baseline, Week 2, **Week 4**, Week 12, Week 26, Week 52

Suicide Risk Assessment

Always ask questions 1 and 2.

1.) Since we last spoke, have you felt as though you wished you were dead?

Yes No

2.) Have you had any actual thoughts about killing yourself?

Yes No

If **YES** to 2, ask questions 3, 4, 5, and 6.
If **NO** to 2, skip to question 6.

3.) Have you been thinking about how you might do this?

Yes No

4.) Have you had these thoughts and had some intention of acting on them?

Yes No

5.) Have you started to work out or worked out the details of how to kill yourself? Did you intend to carry out this plan?

Yes No

***Always ask question 6**

6.) Have you done anything, started to do anything, or prepared to do anything to end your life?

Yes No

Any YES indicates that someone should seek behavioral healthcare.
However, if the answer to 4, 5, or 6 is YES, get immediate help: Call or text 988, call 911, or go to the emergency room. STAY WITH THEM until they can be evaluated.

The study physician will administer the assessment at all appointments. If the patient has a positive response characterized as "High Risk" as per the table, the study physician will take the appropriate clinical action, such as taking the patient to the emergency room, admitting the patient, or deciding to monitor them more closely. To maintain and improve patient safety, we are now formalizing the administration of the Columbia Suicide Severity Rating Scale (C-SSRS), an assessment used in Columbia University Irving Medical Center psychiatry clinical facilities including the Emergency Room. This will be documented in the patient's chart. If responses to questions 1 and 2 in the 6-item scale are "no", the rater skips to question 6. If the answer is "yes" to question 2, questions 3-6 are asked. Any "yes" on the scale indicates that someone should seek behavioral healthcare and the research team will ensure that this occurs. Further, if the answer to any of the items of 4, 5, 6 is "yes", immediate action will be taken by the study physician, which involve the patient being taken to the Emergency Room or calling 911. This will be documented in the patient's chart and an SAE will be submitted to the IRB. Based on the clinical situation, the study physician will decide, in conjunction with the study PI (Dr. Devanand), if this should be reported as a Serious Adverse Event to the IRB, e.g., if the patient is hospitalized for suicidality. If the patient is hospitalized, the patient will be told to interrupt the study treatment, valacyclovir or placebo. Of note, there is no evidence that valacyclovir use is associated with increased suicidal ideation. If treatment interruption occurs, treatment with study medication can be resumed within 6 weeks (as per the protocol) if the patient no longer is deemed to be high risk for suicide based on repeat administration of the same suicide assessment that is used at CUIMC facilities. Non-clinical staff (e.g. research assistants) may become aware of suicide risk via routine phone calls and visits with the patient. If a non-clinical staff member is made aware of suicide risk they are required to immediately report suicide risk to the study physician available. There is a rotation for a study physician on call, which is constant each week, and when the study physician is not in, this authority is automatically delegated to Dr. Devanand who is available 24/7. If the non-clinical staff member is made aware of the suicide risk outside of MDC clinic hours, they are required to report the suicide risk to Dr. Devanand, who is available for contact at all times (i.e., 24 hours/day, 7days/week). When Dr. Devanand is not available he

signs out coverage to another study physician. There is a rotation for a study physician on call, which is constant each week, and when the study physician is not in this authority is automatically delegated to Dr. Devanand who is available 24/7.

Exact wording in SRMP Checklist is as follows:

ITEM	RESPONSE	Comments/Note
A. Which of the Study Types best describes your study	1, 2, 3, 4, 5	3
B. Describe your study population in terms of risk for suicide compared to the general population	Higher, Lower Same As Not known	Slightly higher in some published studies, same as in other published studies.
C. Describe any part of your study or procedures that could increase suicide risk in your study population	Such as: delay to treatment, medication taper/discontinuation, Placebo control design, other	N/A
D. Are you using score on the C-SSRS as an Exclusion?	No/Yes. If yes, provide rationale	We are using this scale to determine exclusion and we take both patient and caregiver responses into account when completing the scale. If responses to questions 1 and 2 in the 6-item scale are “no”, the rater skips to question 6. If the answer is “yes” to question 2, questions 3-6 are asked. Any “yes” on the scale indicates that someone should seek behavioral healthcare and the research team will ensure that this occurs. Further, if the answer to any of the items of 4, 5, 6 is “yes”, immediate action will be taken by the study physician, which involve the patient being taken to the Emergency Room or calling 911. This will be documented in the patient’s chart and an SAE will be submitted to the IRB.
1. Use of 6-item C-SSRS		Yes

1A. How will you be administering the C-SSRS	Describe (e.g. REDCap, phone)	Using the 6-item C-SSRS, the study physician makes a clinical assessment of suicide risk at each study visit throughout the protocol. The study physician will administer the assessment at all follow-up appointments in person or over the phone.
1B. When will be you administering the C-SSRS	This should be at every study contact: list them out	Will be administered in-person at screen, baseline, weeks 12, 26, and 52, and over the phone at weeks 2 and 4.
1C. What threshold score on the C-SSRS will you use to trigger Clinical Coverage		If the C-SSRS score is 4 or greater, it will trigger a clinical response by the study physician who administers the C-SSRS with consultation with the study PI.
2. Arrangements for Clinical Coverage (CC)		Study physicians administer the C-SSRS and they will take clinical action themselves, consulting the PI if needed.
2A. Will research assistants be administering the C-SSRS? If yes, go to 2B		No, only study physicians will administer the C-SSRS.
2B. How they will call in CC		N/A
3. Standards for Clinical Evaluation and Risk Mitigation	Describe	Study physicians administer the C-SSRS and they will take clinical action themselves, consulting the PI if needed.
4. Emergency Contacts	Requested or Required	Required.
5. Indicators for Review for Possible Discontinuation	Operationalize in terms of scores on C-SSRS	A C-SRRS score of 4 or higher at any time will lead to review for discontinuation by the study physician in consultation with the PI and review by the Independent Clinical Monitor.

6. Indications for Independent Clinical Monitor	Describe indications	When a participant's C-SRRS score of 4 has prompted a team review for possible discontinuation, an independent clinical monitor (Psychiatrist) will assess the patient and review with the PI if study discontinuation is warranted.
7. Standards for Documentation of CC		In the research chart, if the C-SSRS threshold criteria are triggered, the study physician who administered the C-SSRS will describe the reason for which the clinical review was activated and what efforts were made by the study physician (with the assistance of the research team) to secure the participant's safety. The note will contain a description of the evaluation including pertinent details of the history obtained, a mental status exam, and description of the assessment of risk and clinical rationale. The note will include the referral process (active or passive) and intent to follow-up. Follow-up should be confirmed in a subsequent note within 72 hours. If the participant has received clinical care from the research team during the study, the evaluation, referrals made, and follow-up also need to be documented in the clinical chart.
8. Standards for reporting AEs and SAEs		Any ER visit for suicidal behavior must be reported as an SAE; any suicide attempt must be reported as an SAE even if it did not result in an ER or doctor visit; a suicide death is an SAE. Further, if the answer to any of the C-SSRS items of 4, 5, 6 is "yes", immediate action will be taken by the study physician, which involve the patient

		being taken to the Emergency Room or calling 911. This will be documented in the patient's chart and an SAE will be submitted to the IRB.
9. Plans for training the research team on the SRMP		Study physicians will do the online training available from the Columbia Lighthouse Project. The lead author of the C-SSRS, Dr. Kelly Posner, is available for individual study consultation and study specific help.
10. Construction of Consent and Assent Forms to reflect SRMP	Follow suggestions in Guidance for Study Type	Suicidality is not a direct research focus and consent forms do not focus on the issue of suicide. Exceptions to this should be discussed with the Protocol Analyst and IRB co-Chairs. Participants should generally be able to continue participation in the study if their suicidality does not require removal and the presence of suicidal symptoms does not interfere with research participation. The stated C-SSRS criteria are consistent with this approach.

Recruitment Procedures

This section will include all information regarding your study's recruitment process/procedures.

Describe settings where recruitment will occur.

The proposed study will be conducted at the New York State Psychiatric Institute, Columbia University Irving Medical Center/NYP and the CU Kreitchman PET center.

The Columbia University ADRC includes a Memory Disorders Clinic and Behavioral Neurology practice with 10 neurologists and geriatric psychiatrists who evaluate over 800 new patients, of whom over 300 have MCI, annually. Over 1400 patients, including over 400 with MCI, are seen in follow-up.

1.) From this source, we expect 44 annual referrals of patients with MCI who previously tested PET amyloid or CSF positive for AD from either clinical workup or other clinical trials. Of these 44 patients, 30 will be HSV seropositive and enter the trial.

2.) We expect 32 patients with MCI without AD-biomarker results to be referred from the same sources, 22 will test HSV seropositive, and of them 10 are likely to be PET amyloid positive and join the trial. Some of these patients were screened ineligible for VALAD because they had MCI and not AD; for those who indicated interest in other research studies, we will contact and screen them for VALMCI.

3.) We expect another 40 patients with MCI to be referred from Internal Medicine (Dr. Luchsinger, collaborator) or via advertising (flyers posted throughout NYSPI/CUIMC campus; ads in local newspapers), 28 to be HSV seropositive, of whom 10 will be PET amyloid positive and join the trial (lower PET+ rate because of broader referral sources).

We recruited 40 HSV+ patients with mild AD for VALAD in 2019; recruiting 50 broadly defined MCI patients in one year is feasible. As in VALAD, the proposed trial is appealing because it involves a novel, unique, understandable mechanism, uses oral capsules rather than I.V. medications, and valacyclovir is very safe.

How and by whom will subjects be approached and/or recruited? Subsequently, referred patients will be approached and recruited by Drs. Devanand, Pelton, Maayan, and Deliyannides (i.e. following referral from the aforementioned sources only).

How will the study be advertised/publicized? A flyer will be submitted to local media to advertise, as well as in medical centers and at caregiver support groups to advertise specifically for the study, and web postings through websites such as www.recruit.cumc.columbia.edu and Facebook.

Attach any ads/recruitment materials requiring review at this time in the Uploads section.

Clinical Trials:

Does this study involve a clinical trial? ☐ No ☒ Yes

Please provide the NCT Registration Number for your Clinical Trial. 04710030

YOU MUST REGISTER AT ClinicalTrials.gov IMMEDIATELY UPON RECEIPT OF IRB APPROVAL AND PRIOR TO ENROLLMENT OF THE FIRST SUBJECT. YOU WILL BE PROVIDED WITH A NCT REGISTRATION NUMBER ON REGISTRATION. PLEASE REVISE THIS SECTION OF THE PROTOCOL SUMMARY FORM TO INCLUDE THE NCT NUMBER AND RE-SUBMIT AS AN AMENDMENT TO THE IRB.

Concurrent Research Studies

In this section, please identify if subjects in this study participate in or will be recruited from other studies.

Describe where subjects are recruited from. After completion of, or screen failure to other studies, and if the patient meets this study's Inclusion/Exclusion criteria, they will be recruited from other studies.

Describe the recruitment source for (Must provide IRB Number, PI and Title). NYSPI IRB Protocols: #7537 (VALAD, PI: Dr. Devanand) and #7672 (NOMAD, PI: Dr. Terry Goldberg).

Inclusion/Exclusion Criteria

This section details your study sample(s) and addresses the requirement for risk minimization.
You may choose to divide your sample by population (healthy controls vs. patient population) or by procedure (subjects who will have an MRI vs. those who will not) and then define different sets of criteria for each.

For each sample, create or insert a table to describe detailed criteria for study inclusion and exclusion and the method you will use to ascertain each criterion. The method of ascertainment may describe tests, scales and instruments. When relevant, indicate the level of training of the person who will make the assessment (e.g. clinical interview by a psychiatrist).

Inclusion/Exclusion Criteria need to be numbered and listed in outline form (see Table template below).

Name the subject group/sub-sample

CRITERION	**METHOD OF ASCERTAINMENT**
Inclusion:	
1. English and Spanish speaking males and females age 50-95. Females must be post-menopausal, defined as 12 consecutive months without menstruation.	Patient Report
2. Diagnosis of MCI (includes eMCI and lMCI by ADNI criteria, defined by scores greater than 1 SD below norms on Logical Memory II Story A Delayed Paragraph Recall: 9-11 if greater than 16 years of education, 5-9 for 8-15 years of education, 3-6 for 0-7 years of education).	Neuropsychological Evaluation
3. Folstein Mini Mental State (MMSE) greater than or equal to 23/30.	Neuropsychological Evaluation
4. Patient retains capacity to consent for him/herself or retains the capacity to identify a surrogate who will consent on his/her behalf.	Physician Evaluation
5. At screening, patients must test positive for serum antibodies to HSV1 or HSV2. Patients that test equivocal (index between 0.90-1.09; <0.90 is negative and > 1.09 is positive) will count as positive.	Laboratory Tests
6. Use of cholinesterase inhibitors or memantine is not required but will be permitted. If already prescribed, doses of these medications must be stable for 1 month prior to study entry. Patients are permitted to receive	Patient Report

cholinesterase inhibitors and/or memantine throughout the duration of the study. Any changes to the medication will be documented in the participant research chart. Medications given for other medical reasons, e.g., antidiabetic or anti-hypertensive medications, will not be altered for the purposes of this trial and the patient's primary physician may adjust such medications as medically indicated throughout the trial. Psychotropic and other medications are allowed. Details of concomitant medication use will be documented at all visits and will be available for statistical analysis.	
7. Either PET amyloid scan positivity or prior CSF biomarker positive for AD (Aβ42 and tau/p- tau).	Medical Records or through completing a PET Scan as part of screen
8. A family member, friend, or other individual who is in contact with the patient agrees to serve as the patient's informant during the study and signs the "Informant Information Sheet."	Patient Designation
Exclusion:	
1. Current clinical diagnosis of schizophrenia, schizoaffective disorder, other psychosis, bipolar disorder or current major depression by DSM-5 criteria. Prior history of major depression will not be exclusionary (25% of older adults have a lifetime history of major depression).	Physician Evaluation
2. Active suicidal intent or plan.	Physician Evaluation with SRMP Assessment
3. Current or recent (past 6 months) alcohol orsubstance use disorder (DSM-5 criteria).	Physician Evaluation
4. Current diagnosis of other major neurological disorders, including Parkinson's disease, multiple sclerosis, CNS infection, Huntington's disease, and amyotrophic lateral sclerosis.	Physician Evaluation
5. Clinical stroke with residual clinical deficits. MRI findings of cerebrovascular disease (small infarcts, lacunes, periventricular disease) in the absence of clinical stroke with residual neurological deficits will not lead to exclusion.	Physician Evaluation
6. Acute, severe, unstable medical illness. For cancer,	Physician Evaluation

patients with active illness or metastases in the last 12 months will be excluded, but past history of successfully treated cancer will not lead to exclusion.	
7. Sitting blood pressure > 160/100 mm Hg.	Physician Evaluation
8. Renal failure as determined by an estimated Glomerular Filtration Rate (GFR) < 44 ml/min/1.73m2 (see 4.3.b.).	Laboratory Report
9. Serum vitamin B12 levels below the normal range.	Laboratory Report
10. Patients with thyroid stimulating hormone (TSH) levels above 4.94 mIU/L.	Laboratory Report
11. Use of benzodiazepines in lorazepam equivalent doses equal to or greater than 2 mg daily.	Patient Report
12. For MRI, metal implants and pacemaker, and claustrophobia such that the patient refuses MRI. In our experience, these exclusions occur in less than 5% of patients with mild AD. MRI is required.	Patient Report
13. Radiation exposure in the prior 12 months that, together with 18F-- Florbetapir will be above the FDA annual radiation exposure threshold. This will be determined through study staff (i.e. Principal Investigator, Study Physician) discussion with potential subjects at Screening, documenting inquiry about radiation history. If there is any history of additional radiation exposure in the past year; it will be reviewed with PET Center staff.	Patient Report and Physician Evaluation
14. Severe vision or hearing impairment that would prevent the participant from performing the psychometric tests accurately. This will be a clinical determination by the study physician without formal testing or audiometry.	Physician Evaluation

Consent Procedures

Explain, in this section:

Explain the consent procedures for this protocol.

Voluntary written informed consent will be obtained from all subjects and their informants by Drs. Devanand, Deliyannides, Maayan, and/or Pelton.

All patients at enrollment will be assessed for capacity to consent and this will be documented in the chart.

The Consent Form describes the nature of the procedures and time requirements, potential risks, the confidentiality of information, and the rights of research participants, including their right to withdraw from the research at any time without loss of benefits to which they are otherwise entitled. It is made explicit that this protocol involves randomized, double-blinded treatment with valacyclovir or placebo with return visits at specified time points, with a description of the research assessments. The consent process also includes documentation of permission to obtain previous medical records.

The IRB-approved forms for Informed Consent and Assessment of Capacity are made part of the patient's permanent medical record and a copy is filed in the participant's research chart.

The study physician obtaining consent signs a Consent Procedure Note, documenting that research procedures and consent forms have been discussed with the patient, the patient understands what is required of them, and would like to participate in the study.

The Consent Procedure Note has been expanded for the Study Physician to indicate whether or not the participant agreed to the storage of biological samples and future use of such data.

Specific consent issues and risks pertaining to apolipoprotein E genotyping are described in the sections below.

If the eligibility screening for this study is conducted under a different IRB protocol, enter the NYSPI IRB# N/A.

Waiver of Consent / Authorization

The following sections are to be completed for the appropriate waiver/alteration of consent.

Waiver of Consent for use of Protected Health Information (PHI)

What records do you wish to review?

What information are you seeking access to?

Describe your plan to protect identifiers from improper use and disclosure.

Describe your plan to destroy the identifiers as soon as possible, consistent with the conduct of the research, or provide a health or research justification for retaining the identifiers or explain how retention is required by law.

Explain why the research could not be practicably carried out without the information (for which you are requesting access).

Explain why the research cannot be practicably carried out without the waiver.

Explain how/if subjects will be provided with additional pertinent information after participation.

Justification for Waiver or Alteration of Consent

Waiver of consent is requested for the following.

Explain why your research cannot be practicably carried out without the waiver or alteration.

Describe whether and how subjects will be provided with additional pertinent information after participation.

Waiver of Documentation of Consent

Would the consent form signature be the only link between the subject's identity and the research data?

Is breach of confidentiality the main study risk?

Is consent for this research procedure ordinarily not required outside of the research context? Explain.

Describe the study component(s) for which waiver of documentation is requested.

Waiver of Parental Consent

Explain why parental/guardian consent is not a reasonable requirement to protect the minor participants in this study.

If parental consent is waived, describe a mechanism that will be substituted to provide appropriate protections for the subjects.

Assent Procedures

In this section, please describe the procedures by which subject assent will be assessed and / or recorded.

Participants who respond to outside advertising will complete a telephone screen prior to completing a screening visit in the clinic.

Participants referred to the study will undergo a screening process (MMSE) and initial check for inclusion/exclusion criteria (previous positive AD biomarkers via 18F-Florbetapir Amyloid PET or CSF studies; diagnosis of MCI by ADNI criteria described in formal Inclusion Criteria). If the patient appears eligible based on screening, a study physician will confirm by patient interview

that all inclusion/exclusion criteria are met, and they will go over the details of the study with the patient as described in the informed consent form.

Patients will be given ample time to review the consent forms and will be given the opportunity to ask questions. Patients will sign the official study informed consent and HIPAA Authorization at Screening. The Consent Form Summary will also be presented to the patient at Screening, but doesn't require signature.

Patients with MCI are expected to be able to consent for themselves and surrogate and/or informant consent are not required.

The individual obtaining consent will explain that if travel does not seem safe, the study visit(s) can be rescheduled.

At Screening, Principal Investigator and/or Study Physician will review prior radiation exposure with potentialsubjects. This information will be reviewed with PET Center staff for their approval before proceeding with recruitment. Only Drs. Devanand, Pelton, Deliyannides and Maayan will obtain consent from participants.

Informants: In our prior studies, 92% of patients had at least one informant available for interview. Most informants provided information by telephone interview. In the proposed study, we will use this approach for informants who cannot accompany the patient to visits. Informants will be asked questions regarding the participant's social and everyday functioning, as well as questions regarding the participant's memory. These involve standardized rating scales as described in further sections of the PSF. Research coordinators will obtain written informed consent from the informant to provide this information during the study using the "Informant Information Sheet" attached to the participant consent form. Informants will solely be interviewed to provide information about study participants, and will not be providing any information about themselves beyond basic contact information.

The IRB-approved forms for informed consent and for assessment of capacity are made part of the patient's permanent medical record, with a copy being filed in the research chart.

Throughout the study, the study physicians will cross-cover each other for patient assessments and management in the study. All study physicians are board certified psychiatrists and their clinical role is to serve as the study physicians.

Memory Disorders Clinic: Memory Disorders Clinic study physicians, who work in a supervisory capacity or follow patients whom they have seen for a long period of time. New evaluations are conducted by Neurology fellows. If a patient is potentially eligible, these fellows will briefly describe the study and if the patient isinterested then refer the patient to Drs. Devanand or Deliyannides or Pelton or Maayan who will screen and recruit the patient if eligible.

Behavioral Neurology Practice Group: Physicians who are part of the Behavioral Neurology Practice Group evaluate a patient who may be eligible, respective physician will explicitly inform patient that they have the option of getting a second opinion regarding study participation, from a physician in the clinical setting, who is not an investigator in the study and immediately arrange for that second opinion if requested.

Persons Designated to Discuss and Document Consent

Please list all the names of persons designated to obtain consent / assent. All persons must complete CITI training for NYSPI. The PI affirms that each name listed has completed the appropriate training.

Deliyannides, Deborah, MD

Devanand, Davangere, MD

Maayan, Lawrence, MD

Pelton, Gregory, MD

Independent Assessment of Capacity

This section is designated for those studies that have been identified where subjects May Lack capacity to consent.

Describe the Methods/procedures for capacity assessment. Patients with amnestic MCI (eMCI or lMCI) with Folstein MMSE score greater than or equal to 23/30 at screening will sign consent to participate in the protocol, and all patients will be required to have the capacity to consent to enroll in the protocol. All informants will be required to sign the "Informant Information Sheet" to indicate that they agree to the responsibilities detailed in the document. The study lasts 12 months (52 weeks) or one year, for each participant.

If your study involves subjects who DO LACK capacity to consent, please justify. All patients are required to have the capacity to consent at their screening visit, as this is consistent with a diagnosis of MCI.

The following approach will be used during the 12-month trial. If the Folstein MMSE declines to below 18 out of 30 at any time-point during the trial, an independent assessment of capacity will be conducted. If the independent assessor determines that the patient retains the capacity to participate in the study, the patient will continue in the study. If the patient no longer retains the capacity to consent in the study, then the patient will be asked to assent to continued participation and to also agree that the surrogate designated by the patient will continue to act in this capacity. If both these criteria are met, the patient will continue in the study. If both these criteria are not met, the patient will be withdrawn from the protocol.

Procedures for surrogate consent. For NYSPI/Columbia, New York State regulations regarding capacity to consent, as utilized by the New York State Psychiatric Institute IRB, will be followed. Under no circumstance will a patient objecting to participation be included in the study.

1. A psychiatrist or licensed clinical psychologist who is independent of the research must confirm that the patient still retains the capacity to designate a surrogate, i.e., identify the surrogate and indicate that the surrogate can consent on the patient's behalf for the research study. Dr. Nancy Kerner will be the independent evaluator for this study. She will follow the procedures described below, using the PCS forms attached, as an addendum to the Informed Consent Form.
2. The document designating the research surrogate must be witnessed by two persons who are independent of the research. The psychiatrist or licensed clinical psychologist who assesses the patient's capacity to choose a surrogate may also be witness to the choice of the surrogate.
3. If the patient chooses a surrogate but is unable to sign the document, another person may sign for the patient and the two witnesses shall, in writing, confirm the patient's choice of a surrogate and witness the signature of the person signing for the patient.
4. The surrogate cannot function as a witnessto the choice of the surrogate. A family member or friend of the patient who is not the surrogate may function as a witness.

5. The surrogate cannot be an administrator or employee of the facility at which the research is conducted or the facility conducting the research. This restriction does not apply if the person is related to the patient by blood, marriage, or adoption. The selection of a patient's spouse as a surrogate is revoked upon the legal separation or divorce of the patient and spouse unless the patient specifies otherwise.
6. Notice of the appointment of a surrogate must be provided to the Mental Health Legal Service (MHLS). We will inform MHLS each time a patient who lacks capacity to consent and appoints a surrogate is recruited for this protocol.

Study Procedures

Provide a clear, concise narrative of study procedures with special attention to the subjects' involvement. Detail the overall study timeline and location of study procedures, list all interventions, assessments and interviews, estimate the duration of each procedure, provide dosing schedules, identify study personnel involved in each procedure, and provide credentials for relevant personnel. If treatment is provided, specify the minimum credentials for providing that treatment. For complicated study designs, we strongly encourage attaching tables, flow-charts, and study algorithms.

Columbia University Medical Center/New York State Psychiatric Institute

Dr. Davangere Devanand, MD: Dr. Devanand will be the Principal Investigator and a study physician. He will advise and back up Dr. Pelton, forthe patientsthat they treat and follow during the study. Dr. Devanand is responsible for making diagnostic judgments for all patients at baseline and at subsequent major time points. He is also responsible for the conduct and coordination of all procedures, all study personnel and the supervision of research assistants. He will liaison with Dr. Howard Andrews, who will be responsible for managing the database. He assumes final responsibility for data analysis, presentation of results and writing of publications for this project. He will train and maintain ongoing reliability with Dr. Pelton on rating instruments and supervise the research assistant on the administration of relevant rating scales.

Dr. Gregory Pelton, MD: Dr. Pelton will be a study physician. He will evaluate the patients during the visits and be responsible for the clinical care of the patients during the course of the study.

Dr. Deborah Deliyannides, MD: Dr. Deliyannides will be a study physician. She will evaluate the patients during the visits and be responsible for the clinical care of the patients during the course of the study.

Dr. Lawrence Maayan, MD: Dr. Maayan will be a study physician. He will evaluate the patients during the visits and be responsible for the clinical care of the patients during the course of the study.

Jeffrey Motter, Ph.D: Dr. Motter has used Freesurfer to analyze/publish MRI data; he will conduct and publish the MRI cortical thinning analyses.

John Mann, MD: Dr. Mann, Professor of Psychiatry and Radiology, has broad expertise in the technical and applied aspects of PET imaging in brain disorders. He will act as a co- investigator, and willsupervise and lead the PET image analysis team.

Francesca Zanderigo, PhD: Dr. Zanderigo is a Bioengineer whose focus is extraction of accurate quantitative information from medical images. She will be responsible for quantification of all PET data and contribute to reports and manuscripts.

Dr. Howard Andrews, PhD: Dr. Andrews will serve as the Database Manager. He is a highly experienced database manager and programmer who has functioned in these roles for several research studies. With his team, he will help to develop the forms used in the study in collaboration with Dr. Devanand, program the computers for data entry, develop algorithms for range checking and logical checking, and prepare programs to generate reports to the Principal Investigator regarding subject accrual, follow-up scheduling, and error checking. Dr. Andrews will work closely with the research staff to make any necessary corrections to the database and will maintain an audit trail documenting these changes. Dr. Andrews will arrange for backup of all project data and for verification of database integrity. He will do the required programming to create output files in SPSS or SAS format to the investigators.

Cileyn Herrera: Ms. Herrera willserve as the administrative program manager for this study.

Dr. Edward Huey, MD: Dr. Huey was a study physician who left the department. He evaluated the patients during the visits and was responsible for the clinical care of the patients during the course of the study.

Renjie Zhang: Ms. Zhang will act as Research Assistant, and will assist in recruiting half the sample, conduct neuropsychological testing and interviews, ensure collection of blood (apoE genotyping) with serum and plasma separation (viral antibodies and proteomes), coordinate/schedule MRI and PET scans, and conduct/coordinate data entry and outputs with data management.

Sansara Mahtani: Ms. Mahtani will act as Research Assistant, and will assist in recruiting half the sample, conduct neuropsychological testing and interviews, ensure collection of blood (apoE genotyping) with serum and plasma separation (viral antibodies and proteomes), coordinate/schedule MRI and PET scans, and conduct/coordinate data entry and outputs with data management.

Gillian Monty: Ms. Monty has since left the Memory Disorders Clinic and will not have any interaction with the study participants moving forward. She previously acted as a Research Assistant, and assisted in recruiting half the sample, conducted neuropsychological testing and interviews, ensured collection of blood (apoE genotyping) with serum and plasma separation (viral antibodies and proteomes), coordinated/scheduled MRI and PET scans, and conducted/coordinated data entry and outputs with data management.

Andy Sanchez, MD: Dr. Sanchez will act as a Research Assistant, and will assist in recruiting half the sample, conduct neuropsychological testing and interviews, ensure collection of blood (apoE genotyping) with serum and plasma separation (viral antibodies and proteomes), coordinate/schedule MRI and PET scans, and conduct/coordinate data entry and outputs with data management.

Jamie Graff: Ms. Graff will act as a Research Assistant, and will assist in recruiting half the sample, conduct neuropsychological testing and interviews, ensure collection of blood (apoE genotyping) with serum and plasma separation (viral antibodies and proteomes), coordinate/schedule MRI and PET scans, and conduct/coordinate data entry and outputs with data management.

Betty Ostrager: Ms. Ostrager will act as a Research Assistant, and will assist in recruiting half the sample, conduct neuropsychological testing and interviews, ensure collection of blood (apoE genotyping) with serum and plasma separation (viral antibodies and proteomes), coordinate/schedule MRI and PET scans, and conduct/coordinate data entry and outputs with data management.

PCP/Outside Providers:

All patients are required to have a primary care physician or outside medical provider who can manage their clinical treatment and non-study related prescriptions throughout the duration of the study.

MRI:

Structural image Analysis at NYSPI/Columbia for MRI acquired MRI (Baseline and Week 52) will be conducted in the NYSPI MRI facility and the Mortimer B. Zuckerman Mind Brain Behavior Institute (a Columbia University Medical Center Facility).

MRI acquisition sequences will follow the ADNI protocol for GE scanners (3T) that have been used: http://adni.loni.usc.edu/methods/documents/mri-protocols/. Using each individual's T1-weighted image, global and regional measures will be derived using FreeSurfer 5.3 software package (http://surfer.nmr.mgh.harvard.edu/). Freesurfer automatically assigns a neuroanatomic label to each voxel with accuracy comparable to manual labeling. A set of volumetric ROIs is thus defined. The estimation procedure is automated but is visually checked for accuracy of spatial registration and borders of white matter and gray matter segmentations as per the analytic procedures described. Calculated volume within each region is adjusted for variationsin the individual's intracranial brain volume measured by BrainWash (automatic multiatlas skull-stripping software package). We will process the longitudinal T1-weighted images using the FreeSurfer longitudinal pipeline, recently implemented to detect small changes over time. This processing pipeline isrobust to initialization points, which often generate small variations in results of the optimization processes. This is done by initializing the processes for a new data set with results of the already processed unbiased template.

PET 18F-Florbetapir Imaging:

PET 18F-Florbetapir will be conducted at the Kreitchman PET Center at Columbia University Medical Center for subjects at Screening or Baseline and Week 52.

18F-Florbetapir is purchased from PETNET. The PET technical team is highly experienced in the use of this commercially available tracer.

Phantom scanning is not required. Arterial lines are not placed in this project.

EKG:

For all participants who are age 60 years or older, an EKG will be completed at baseline, or at the next visit time point for all active study participants. EKGs will be completed at baseline for 2 patients currently pending their baseline visits. For all currently active patients who have already completed their baseline visit, an EKG will be completed at their next in-person visit (Week 12 or 26 or 52). EKGs will only be repeated at the subsequent study visits if an abnormality is present during the patient's initial EKG. All EKG abnormalities will be reviewed with the patient's primary care physician (all patients have an outside primary care physician). The patient's primary care physician and the study team will work together to determine whether any action is indicated and if it is safe for the patient to continue in the protocol. While the study medication Valacyclovir does not have any listed cardiac side effects neither in its medlineplus.gov web page https://medlineplus.gov/druginfo/meds/a695010.html nor in its package insert https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/020487s007rel2_lbl.pdf, acyclovir, which is what Valacyclovir is converted into after first pass metabolism, does have Tachycardia listed as a rare side effect in its medlineplus.gov information page https://medlineplus.gov/druginfo/meds/a681045.html. While we obtain heart rate at each in-person study visit, we will obtain this reading, more precisely, from the EKG and act on it as follows: any patient with a measure of heart rate over 100 beats per minute will be asked to suspend their administration of study medication in the study and await clearance by their primary care physician for re-entry into the study.

Computer and Database Facilities - Data Coordination:

The data collected in this study will be entered and monitored by the Database Management Unit at NYSPI. This unit is headed by Dr. Howard Andrews, whose unit has 2000 square feet of office space, and can easily accommodate the data management activities in this proposal.

The unit will work closely with the research assistant/coordinator and the Principal Investigator to facilitate independent auditing of primary subject records. The database will provide reports indicating all modifications that have been made in the database together with paper communications (fax, e-mail) confirming and authorizing these modifications.

Access to the data system is available only to authorized users, with multiple levels of security including User ID/password authentication via MS Active Directory overseen by experienced IT personnel.

Additional security is provided by SIR software. Authorized users will include one and at most two research assistants/coordinators who will conduct data entry; the only other authorized users with direct accessto the data system will be data coordinating center (DCC) staff. DCC data-related operations and the SIR/Citrix system have been certified by Columbia University's Information Security Office.

All Consent forms and HIPAA forms are paper documents and require wet signatures; electronic signatures are not used.

PHONE SCREEN

Some participants are referred directly, e.g., from another completed study in the same clinic, and Phone Screening is not done. For others, Phone Screening is done. The phone screen will be completed by research coordinator to determine initial eligibility of a participant prior to scheduling a screening visit. Verbal consent will be obtained and documented on the Phone Screening Worksheet prior to requesting PI/PHI from the potential participant. Phone screening forms will be saved on the secure NYSPI server and filed in the participant's chart when applicable.

SCREENING VISIT

At the time of screening at NYSPI the patient will be evaluated by a treating physician and diagnosed. This evaluation will include a complete physical exam. A brief, standardized neurological and psychiatric evaluation will be completed including administration of Logical Memory I and II by the research coordinator, as part of the MCI diagnostic evaluation (per Inclusion/Exclusion Criteria). In addition, the MMSE will be administered by the research coordinator at the initial evaluation. If the patient meets protocol inclusion and exclusion criteria and is willing to participate, the study physician will obtain informed consent and the CDR (sum of boxes) will be administered by the study physician. Medical records will be obtained from the subject's primary care or referring physician, as needed. The study physician will document the study visit in a typed progress note.

Blood will be collected for serum anti-HSV antibodies with quantitative IgG and IgM as well as HHV6A and HHV6B; HHV 7; SMAC blood chemistry and Complete Blood Count.

If all aforementioned screening assessments and procedures are completed, and key inclusion criteria are met, the research coordinator will schedule screening 18F-Florbetapir PET scan only following confirmation of all key inclusion/exclusion criteria, as determined by PI and/or Study Physician.

SUVR > 1.15 (results reported within 5 days after scan) will be required for study entry. In our clinic and industry drug trials, PET amyloid scans and/or CSF is obtained to assess low Aβ42 and high tau/p-tau with standard biomarker criteria for AD. If prior PET amyloid scan or CSF was AD-positive, the patient will be eligible, but will still have to complete an Amyloid PET scan at Baseline visit. Medical records will be required for verification if prior Amyloid PET and/or previous CSF AD Biomarker results are used to confirm study eligibility. If AD biomarker positive medical history cannot be confirmed, the Amyloid PET will take place as a screening procedure.

As part of the screening evaluation, a comprehensive history will be taken to include age, age-at-onset of memory problems, handedness, education, occupation, medical and psychiatric history.

As described in the consent forms, all clinically applicable information collected during the trial will be disclosed to patients, as well as interpretation of Baseline MRI and results from clinically relevant lab work and select neuropsychological testing.

After the Baseline evaluation, the results of outcome measures specified in the hypotheses will not be disclosed. Apolipoprotein E genotyping results will not be disclosed nor will results of viral proteome and antibody assays.

Throughout study weeks (baseline, weeks 0, 2, 12, 26 and 52), remote administration of measures (interviews and/or select neuropsychological testing) may be carried out. Research interviews and rating scales will be administered to the patient by the research coordinator and the study physician. These are done over the telephone prior to each clinic visit in order to minimize time spent in the clinic. Interviews and rating scales are done over the telephone because visual examination of the patient is not required. Clinic visits are necessary because neuropsychological testing and blood draws take place throughout protocol, and at specific visits, other procedures like MRI and PET are required.

BASELINE/WEEK 0 VISIT

Patients who are enrolled will be asked to come for the baseline visit, typically 1 week after the screening visit.

These guidelines and procedures will be followed:

Procedures Completed with CU/NYSPI Collaborators:

At Baseline (as well as at Screening and Week 52) procedures conducted with collaborators (MRI at Mind Brain Behavior Institute [MBBI], NYSPI MRI suite, CU PET) will follow each facility's existing, and in the future, updated regulations

Staff will follow established workflows and guidelines being implemented with collaborating CU facilities using EPIC EMR, for scheduling subject study procedures.

Necessary paperwork will be scanned and emailed to facility staff 24 hours in advance of scan/procedure.

Study participants will arrive as scheduled at the facility by private vehicle or Uber/Lyft (reimbursed by grant).

Participants will be scheduled so that there is no overlap between participants in the waiting area.

Participants need to move only once from NYSPI clinic space to another scheduled scan/procedure location (NYSPI MRI, CUMC PET), as needed. Subject and informant will then depart directly from the scan/procedure location to go home: they will not be permitted to return to the NYSPI clinic space.

The following scans will be conducted: MRI (baseline and week 52) and 18F-Florbetapir PET (screening or baseline and week 52).

For participants at baseline or at end-trial/week 52, MRI is conducted at NYSPI with a small minority of participants having both MRIs done instead at MBBI (CU space). Research staff will meet the subject/informant at the facility entrance (NYSPI lobby or CU/CUMC facility entrance).

If transport of participants is required within NYSPI (when going to NYSPI MRI suite or PET, from Pardes 1500 area clinic space), the shortest route will be taken to get to target destination. Informants will not be permitted to attend actual MRI scan, and will wait in facility waiting room, unless there is an emergency.

At NYSPI MRI suite specifically, staff and participants will follow all guidelines stated in the “NYSPI MRI Research Program” Handbook.

For PET, staff will not be permitted to enter the suite at all, unless there is an emergency, but the informant may wait in the PET Suite waiting room. The PET Center implements its own “Infection Prevention and Control” document requirements; study research staff are not involved in its implementation and are not permitted to enter the PET Suite.

Research Coordinator will remain at MBBI MRI or NYSPI MRI suite through completion of scan and will escort subjects/informants to exit and go home. Subject and informant will depart from PET Center independent of research coordinator, with instructions to call coordinator to confirm departure for home.

18F-Florbetapir PET will be conducted at the Kreitchman PET Center. For 18F-Florbetapir PET, subjects will undergo IV placement for injection of tracer, followed by a 50 minute tracer uptake time and 20 minute scan.

At time of Baseline, the patient will be clinically assessed by the Study Physician (symptom driven physical exam will be performed, and vital signs collected).

An EKG will be completed for all participants who are age 60 or older at baseline.

Neuropsychological testing and rating scales will be completed. The PACC; UPSIT; ADCS-ADL-PI; UPSA; NACC Physician Evaluation and the CIBIC-Plus-Clinician's Interview-Based Impression of Change will be completed.

Pertaining to neuropsychological tests: research coordinator will place the materials on the clinic room desk and then guide the subject to complete the test, including verbal and written responses required for specific tests, from a distance greater than six feet whenever possible. If a clinic room with more than 6 feet of distance between tester and subject is not available, a conference room will be used.

When neuropsych tests are complete, subject will be instructed to place all testing materials in a tray, which study staff will have placed on the desk prior to the visit session. At end of session, research coordinator will perform hand hygiene after interacting with materials handled by subjects. Non paper testing material will be disinfected with SaniCloth or Clorox wipes immediately after session

Adverse events will be collected and documented by the Research Assistant, for review and follow up between the patient and Study MD. The study physician will document the study visit in a typed progress note.

Blood will be drawn for the following laboratory analyses: Apolipoprotein E genotype; viral proteome and antibody assays and plasma biomarkers t-tau and Neurofilament Light (NFL) as well as extra serum and plasma.

As indicated in preceding section, structural baseline MRI will be completed at NYSPI MRI Suite, or at CU's MBBI facility. If the subject had positive, veritable medical records indicating AD biomarker positivity (via historic Amyloid PET or CSF) for confirmation of inclusion/exclusion criteria, the patient will complete an 18F- Florbetapir PET scan at Baseline.

At this time patients will receive 2-4g of valacyclovir. The oral valacyclovir will be distributed in 500mg pills, so patients will take 4-8 pills per day. Participants are randomized to receive either valacyclovir or placebo. Valacyclovir is titrated from 2g to 4g daily over 4 weeks, with initiation of 2g daily dosing at Baseline. Dosing is monitored by the Study Physician. The maintenance dose of valacyclovir is 4g daily per protocol, for the rest of the 52 week trial. If the participant cannot tolerate the dose of 4 g daily, they can continue to receive active medication treatment as long as they receive at least 2 g daily. Patients will be asked to return the pill bottles with any remaining pills at following visits. The research assistant will record the number of returned pills to confirm adherence to medication procedure.

2-WEEK VISIT (Telephone Call)

The telephone call at 2 weeks is primarily a clinical call to monitor the patient's status on valacyclovir/placebo 2 g/day and raise it to 3 g daily (at 2 weeks).

The patient will be clinically assessed by the Study Physician by telephone.

Adverse events will be collected and documented by the Research Assistant, for review and follow up between the patient and Study MD. The study physician will document the study visit in a typed progress note.

4-WEEK VISIT (Telephone Call)

The telephone call at 4 weeks is primarily a clinical call to monitor the patient's status on valacyclovir/placebo 3 g/day and raise it to 4 g daily. Targeted dose is 4 g daily.

The patient will be clinically assessed by the Study Physician by telephone.

Adverse events will be collected and documented by the Research Assistant, for review and follow up between the patient and Study MD. The study physician will document the study visit in a typed progress note.

12-WEEK VISIT

The patient will be clinically assessed by the Study Physician (symptom driven physical exam will be performed and vital signs collected).

An EKG will be completed for all participants who are age 60 or older, if they did not receive one at their baseline visit.

Neuropsychological testing and rating scales: the PACC; ADCS-ADL-PI; UPSIT and the CIBIC-Plus- Clinician's Interview-Based Impression of Change will be completed.

Adverse events will be collected and documented by the Research Assistant, for review and follow up between the patient and Study MD. The study physician will document the study visit in a typed progress note.

Blood will be drawn for the following laboratory analyses: SMAC blood chemistry; Complete Blood Count, as well as blood drawn for later analysis of plasma acyclovir levels. Patient will need to return all unused pills.

26-WEEK VISIT

The patient will be clinically assessed by the Study Physician (symptom driven physical exam will be performed and vital signs collected). The study physician will document the study visit in a typed progress note.

An EKG will be completed for all participants who are age 60 or older, if they did not receive one at their baseline visit.

Neuropsychological testing and rating scales: the PACC; CDR (sum of boxes); ADCS-ADL-PI; NACC Physician Evaluation; UPSA and the CIBIC-Plus-Clinician's Interview-Based Impression of Change will be completed.

Blood will be drawn for the following laboratory analyses: SMAC Blood Chemistry and Complete Blood Count.

Adverse events will be collected and documented by the Research Assistant, for review and follow up between the patient and Study MD. The study physician will document the study visit in a typed progress note.

Blood will be drawn for the following laboratory analyses: SMAC blood chemistry; Complete Blood Count, as well as blood drawn for later analysis of plasma acyclovir levels. Patient will need to return all unused pills.

52-WEEK VISIT (End Point or Drop Out Visit)

The patient will be clinically assessed by the Study Physician (complete physical exam will be performed and vital signs collected). Re-evaluation of diagnosis will be completed. The study physician will document the study visit in a typed progress note.

Adverse events will be collected and documented by the Research Assistant, for review and follow up between the patient and Study MD.

Neuropsychological testing: the PACC; UPSIT, CDR (sum of boxes); ADCS-ADL- PI; UPSA; NACC Physician Evaluation and the CIBIC-Plus-Clinician's Interview-Based Impression of Change will be completed.

Physical Activity Assessment Scale will be completed.

An EKG will only be repeated at a patient's final study visit (Week 52) if they presented with an abnormality during their initial EKG.

Blood will be drawn for the following laboratory analyses: serum anti-HSV antibodies with quantitative IgG and IgM; HHV6A and HHV6B; HHV7; viral proteome and antibody assays; SMAC blood chemistry; Complete Blood Count; plasma biomarkers t- tau and NFL, and plasma acyclovir levels.

The following scans will be conducted: MRI and 18F-Florbetapir PET.

Patient will need to return all unused pills.

Time Line: The sample (N = 56) will be recruited over 52 weeks (1 year). After all patients complete the study, the blind will be broken, data analyzed, and manuscripts written. Data entry and cleaning will be done throughout the project and the dataset finalized concurrent with completion of patient participation.

Blindness of raters: Raters will remain blind to randomized treatment condition. The blind will not be broken during the entire trial. In a clinical emergency, the blinded medication (drug or placebo) will be continued if possible; if not, the blinded treatment will be stopped.

Diagnosis: diagnosis of MCI (includes eMCI and lMCI by ADNI criteria, defined by scores > 1 SD below norms on Logical memory II Story A Delayed Paragraph Recall: 9-11 if > 16 years of education, 5-9 for 8- 15 years of education, 3-6 for 0-7 years of education), HSV1 or HSV2 seropositivity, and either PET amyloid scan positivity or prior CSF biomarker positive for AD (Aβ42 and tau/p-tau).

eMCI and lMCI:
Early MCI (eMCI) is a form a Mild Cognitive Impairment as is late Cognitive Impairment (lMCI). EMCI subjects represent individuals with milder degrees of cognitive impairment than the lMCI subjects. Both eMCI and lMCI are subtypes of Amnestic MCI. The difference is defined by patient performance on specific cognitive tests that are used to classify eMCI and lMCI.

lMCI is very similar to amnestic MCI by the original Petersen criteria. eMCI, less impaired than lMCI, was defined in ADNI, and a significant proportion of patients with eMCI decline cognitively, several of whom develop AD (Qiu et al. 2014). Therefore, we will include eMCI. Inclusion criteria for HSV seropositivity ensures targeting of patients who may respond to valacyclovir, and a positive PET amyloid scan (or CSF if done previously) increases the likelihood of AD neuropathology in this broadly defined MCI sample.

Study Duration: If recurrent low-grade infection is causing or contributing to AD, a relatively long duration trial is needed to compare drug to placebo. Peripheral HSV infection recurrence is suppressed markedly by 7 years of continuous valacyclovir, and similarly, valacyclovir in the brain may be disease- modifying by preventing HSV spread after reactivation and/or by treating recurrent low-grade infection. Therefore, 52 weeks is a reasonable trial duration and is feasible within the permitted 2-year project duration.

Total study duration may exceed 52 weeks for those participants encountering delays to in person assessments and/or procedures. Any pause to research activity has, or may be, put into place as part of institutional risk reduction initiative. From a research perspective, this delay will be addressed by evaluating time in study as a covariate in statistical analyses of outcome measures, as appropriate.

Gender and minority: Gender effects will be evaluated in the main analyses. If there are enough subjects in a minority group, their data will be analyzed and compared to the rest of the sample.

Autopsy: Few deaths are expected during the study. Nonetheless, autopsy procedures are available and are organized and highly effective at the Columbia University ADRC.

Clinical Evaluation: History includes chief complaint, referral source, age, age-at-onset of cognitive decline, handedness, education, occupation, medical history, medications used. Alcohol/substance use disorder, head injury, stroke, hypertension, cardiac disease, thyroid disease, other medical conditions, surgery, and recent hospitalization, to be assessed at each visit. Family history of dementia, AD, Down's syndrome, stroke, cardiac disease will be documented.

Physician Evaluation: At the initial visit, the attending physician or designee will use standardized forms to collect an extensive history. We will obtain medical records from the participant's primary care physician or referring physician, as needed. Full physical exam will take place at Screening and 52 Weeks; symptom driven physical exam will be conducted at Weeks: 0, 2, 12, 26 and 52.

Intent to Treat/ Dropouts and missing data: Dropout is estimated at 10% In patients who discontinue study medication, reason for early exit will be documented and study visits will continue at scheduled time- points per the Intent-to-treat (ITT) principle. The primary analyses will be on the ITT sample, i.e., all randomized subjects according to the treatment that they were assigned. Missing data on outcome variables will be dealt with by using (longitudinal) generalized linear mixed effects models that do not require complete measurements under the "missing at random" assumption. For MRI scan and 18F-Florbetapir PET scan, outcomes with just one pre and post measure, inverse probability weighting of cases with complete data will be used where weights are calculated based on the probability of a subject being a completer versus being a dropout. Sensitivity analysis will be performed to provide a range of plausible effect estimates that could arise due to non-ignorable missing data.

Treatment Interruption: treatment interruption for up to 6 weeks will be allowed for medical/surgical intervening conditions.

Data Safety and Monitoring Board (DSMB): A DSMB is required for this study; Drs. Gary Small (Chair), Richard Whitley (member) and Jeffrey Cummings (member) are the individuals selected after consultation and approval from the NIA program staff. This procedure is required for pilot clinical trials in MCI and AD; we have done this before in our recent pilot clinical trials in mild cognitive impairment (MCI) and AD.

For each DSMB meeting or teleconference conducted at the start of the study and every (1) year thereafter, Dr. Howard Andrews who heads the database management team will provide the DSMB with a summary of study progress, SAEs and AEs. He will also provide unblinded data based on the DSMB's preference. The DSMB will make decisions about study continuation, monitor recruitment progress, AEs and SAEs, and provide recommendations to the project P.I. (Dr. Devanand) and his team after each DSMB meeting or teleconference. NIA, and our IRB, will also be provided with the report sent by the DSMB Chair. If SAEs occur in > 10% of the first 20 patients, the DSMB will be approached so that they can guide the research team regarding study continuation.

Criteria for Early Discontinuation

Define criteria that will be used to exit or drop subjects from the study and operationalize. Indicate the time points when such criteria will be applied, and describe the rating instruments, parameters, and thresholds that will lead to a decision to terminate a subject's participation and the role of the person who will make these determinations. Studies which include a medication taper and discontinuation may be asked to include an independent medical monitor (an MD not on the study team) who will aid the study team in determining whether study discontinuation is needed. In addition, explain procedures for managing subjects who are withdrawn from the protocol.

For treatment studies: To minimize risks to subjects, operationalized drop-out criteria should be defined so that subjects who worsen, or in some cases, fail to improve, are removed from the study and offered standard care. The threshold for drop-out should consider the level of risk associated with non-improvement for the specific disorder, the availability of alternatives, and the typical required duration of treatment. For example, emergence of suicidal intent, or psychosis, should prompt immediate clinical evaluation and withdrawal from the study.

The reasons for early discontinuation of a patient from the study are as follows:

1.) Intervening severe medical illness that the PI determines to be grounds for study discontinuation. Medical monitoring is done by the study staff (PI and study physicians; research coordinators gather information and convey any such information to the study physician and PI). All medically relevant decisions are made only by study physicians and the PI. The DSMB monitors the progress of the study including medical issues; all SAEs are reported immediately to the DSMB.

2.) Discontinuation of treatment with valacyclovir or placebo for more than 6 weeks. After an interruption of treatment for any reason, e.g., medical illness, the patient can resume the protocol if the interruption is less than 6 weeks.

3.) Based on the result of a blood draw at the week 12 visit, if the serum creatinine level increases to be greater than 1.5 mg/dl, or eGFR declines to less than 44 mL/min, we will lower the study medication to the minimum dose of 2 g valacyclovir or placebo per day. Patients will then have blood collected and labs repeated at an additional visit, at week 16. If, at week 16, kidney function is still abnormal based on the above criteria, study medication will be discontinued for this patient. The reduction in kidney function will be communicated to the patient's primary care physician.

4.) The patient will be discontinued if 1) the CIBIC-PLUS score is higher than 80 (consistent with moderate dementia or moderate to severe behavioral changes), or if 2) the C-SSRS score is 6 or higher on the Suicidal Ideation Subscale, or if there is any positive score on the Suicidal Behavior Subscale or Behavior Lethality Subscale.

If MRI Acquisition must be terminated for some reason, the patient can still continue in the protocol. This is because MRI outcomes are secondary and not primary.

This is an intent-to treat protocol. Therefore, a patient who is discontinued early in the study due to the above reasons will be followed and evaluated (whenever feasible) until the Week 52 visit, or until the patient withdraws his/her consent to participate.

Blood and other Biological Samples

Describe how the sample will be used and indicate, when relevant, the amount of the sample. The IRB wants to know that the sample is sufficient for the purposes of the study, but that sampling is limited to what is minimally necessary.

If you've indicated that you intend to store a sample for future use, indicate where the sample will be stored, how long the sample will be stored, and to what purposes the sample will eventually be put. Check the IRB website at https://irb.nyspi.org/investigators/guidance/genetic-research for specific guidance and additional information about future use of DNA samples.

Routine Laboratory Tests: At Screening, Weeks 12, 26 and 52, blood will be collected for the following screening laboratory tests, which will be performed by the OMH Clinical Laboratories-Nathan Kline Institute: CBC, BUN, creatinine, eGFR, electrolytes, liver and thyroid function studies, B-12, and folate (a total of 20 mL blood will be collected across all four timepoints).

Serum Antiviral Antibodies and HHV7: At Screening and Week 52, a blood sample will be collected for serum antiviral antibodies to HSV1 and HSV2 with quantitative IgM and IgG. HHV7 will be assessed as part of this panel as well, from standardized assays performed by Quest Diagnostics (8.5 mL blood will be collected at each time point for a total of 17 mL).

Serum HHV6A and HHV6B: At Screening and Week 52, a blood sample will be collected for the analysis of HHV6A and HHV6B. These analyses will be performed by ARUP Laboratories using the quantitative PCR method (8.5 mL blood will be collected at each timepoint for a total of 17 mL).

Apolipoprotein E Genotype Testing: At baseline, a blood sample will be collected for ApoE genotyping (a total of 8.5 mL of blood will be collected). All procedures related to ApoE genotyping were described earlier. DNA will not be extracted and stored for any other genetic testing. These specimens will be sent to the Columbia University HGRC, for storage and plating, and sent to LCG Genomics, for analyses and resulting.

Plasma Acyclovir Levels: At weeks 12 and 52, blood will be drawn for plasma acyclovir levels (7 mL of blood will be collected at each timepoint for a total of 14 mL). These specimens will be sent to Dr. Edward Acosta's Lab at University of Alabama (UAB), for analyses and resulting.

Plasma Biomarkers: t-tau, p-tau epitopes, Neurofilament Light (Nfl): At Baseline and Week 52, blood will be drawn for plasma biomarkers t-tau and Nfl (4 mL of blood will be collected at each timepoint for a total of 8 mL). These specimens will be sent to Quanterix Laboratory, for analyses and resulting.

Viral Proteome and Antibody Assays: At Baseline and Week 52, blood will be drawn for Viral Proteome and Antibody Assays (2 mL of blood will be collected at each timepoint for a total of 4 mL). These specimens will be sent to the Columbia University Lipkin Laboratory, for analyses and resulting.

Extra Plasma and Serum: We will collect blood for storage of extra plasma and serum, at Baseline. A total of 20 mL will be collected for this purpose. Research staff will aliquot specimens accordingly.

A total of 120 mL or 8 tablespoons will be collected per patient for the entire protocol duration.

Assessment Instruments

List all assessment instruments, indicate who will administer them and their credentials/qualifications. Provide an estimate the duration of each measure. The IRB wants to know that assessments instruments are appropriate measures for the purposes of the study and are no more burdensome than necessary. The IRB will consider the burden of assessment instruments (in terms of time, sensitivity of material, etc.) in the risk/benefit analysis. Please attach copies or otherwise provide all non-standard instruments.

Patient Measures

Mini-Mental State Examination (MMSE): The MMSE assesses global functioning and mental status.

Alzheimer's Disease Cooperative Study- Preclinical Alzheimer Cognitive Composite (PAAC): The ADCS–PACC combines four widely used paper-and-pencil cognitive tests. These include the list- learning task from the Free and Cued Selective Reminding Test (FCSRT), as well as a paragraph- recall test from the Wechsler Memory Scale, both of which measure episodic memory. The Digit Symbol Substitution Test from the Wechsler Adult Intelligence Scale tests executive function. The final component, the Mini-Mental State Examination (MMSE), assesses global functioning and mental status.

Alzheimer's Disease Cooperative Study-Activities of Daily Living scale-PI (ADCS-ADL-PI-Self Report): The ADCS-ADL-PI will be administered to the patient, for the assessment of impairments of complex Activities of Daily Living for patients with MCI.

UCSD Performance-based Skills Assessment (UPSA; v.2): The UCSD Performance-based Skills Assessment (UPSA) is a measure of Functional Capacity and assesses skills involved in community tasks. The UPSA-2 includes the following 6 subscales: Financial Skills, Communication, Comprehension/Planning, Transportation, Household Management and Medication Management. Administration time: Approximately 45 minutes

Clinical Dementia Rating (CDR) Sum of Boxes: The formal CDR interview will be used to score 6 domains (boxes); sum of boxes: exploratory outcome. Overall score: 0=none, 0.5=questionable, 1=mild, 2=moderate, 3=severe dementia

National Alzheimer's Coordinating Centers (NACC) Forms: The physician will complete the NACC that takes 35-40 minutes and includes history, neurological exam with assessment of Parkinsonian signs, psychiatric assessment that includes the short version of the Geriatric Depression Scale and the Neuropsychiatric Inventory, Functional Activities Questionnaire (FAQ), vascular risk factors and the modified Hachinski ischemic scale.

UPSIT (Olfaction Assessment): The UPSIT (scratch-and-sniff odor identification test) has been administered to several hundred thousand subjects around the world and its use is not associated with any known side effects. The UPSIT comprises mainly synthetic odors and there is essentially no risk of an allergic reaction with this procedure. If there is an acute upper respiratory infection, testing will be delayed until the participant has recovered.

CIBIC-Plus: Clinician's Interview-Based Impression of Change: this rating scale evaluates global patient function. The CIBIC-Plus includes caregiver input.

C-SSRS: The Columbia Suicide Severity Rating Scale (C-SSRS) is a short questionnaire used to assess a patient's suicidal ideation, intensity of ideation, and suicidal behavior.

Apolipoprotein E (apoE): Apolipoprotein E will be genotyped (ε2, ε3, and ε4 alleles) by LCG genomics using SNPs rs429358 and rs7412. A portion of the blood will be sent out to Prevention Genetics for identification of APOE genotype. Using a standard protocol, DNA is amplified by the polymerase chase reaction (PCR). The genotypes are determined blind to subject status (patient or control) by the sizes of DNA fragments present.

Physical Activity Assessment Scale: a validated 3-item scale, which assesses participants' physical activity level/frequency.

Informant Questionnaires

Alzheimer's Disease Cooperative Study-Activities of Daily Living scale-PI (ADCS-ADL-PI- Study Partner): The ADCS- ADL- PI will be administered to the informant, for the assessment of impairments of complex Activities of Daily Living for patients with MCI.

Functional Assessment Questionnaire (FAQ): The FAQ will be administered to the informant to assess the patient's ability to engage in functional activities.

Please attach copies, unless standard instruments are used.

Sections to be completed for studies using IND/IDE Drugs and Devices.

Prior to the submission of any study involving a faculty held IND or IDE being approved by the IRB, the IND/IDE holder is required to submit a form signed by the IND/IDE holder and PI.

Which are applicable to your study: ☒ Drug ☐ Device ☐ Radiolabeled drug/compound

Off Label and Investigational Use of Drugs

Enter the information for all drugs to be used in this study:

Name of the drug	Valacyclovir
Manufacturer and other Information	We will use the generic version of valacyclovir supplied to the NYSPI pharmacy.
Approval Status (select one)	IND application is pending IND is approved **No IND is required**
IND #	N/A.
Who holds the IND (i.e., IND Sponsor). If other than PI/CU Investigator, type name of holder.	N/A.
Which applies:	**FDA has determined the IND is not required (provide correspondence)** FDA conditions are met (see "Rules") – Explain https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-procedures-investigators-responsibilities

Off Label and Investigational Use of Devices

Enter the information for all devices to be used in this study:

Name of the device	
Manufacturer and other Information	
Approval Status (select one)	IDE application is pending IDE is approved No IDE is required
IDE #	
Who holds the IDE (i.e., IDE Sponsor). If other than PI/CU Investigator, type name of holder.	
Is the device marketed?	
Which applies:	FDA has determined that IDE is not required FDA conditions are met (see "Rules") – Explain https://www.fda.gov/medical-devices/investigational-device-exemption-ide/ide-application Device is "Non-significant risk" – Explain

Off Label and Investigational Use of Radiolabeled Drugs / Compounds

Enter the information for all radiolabeled drug/compounds to be used in this study:

Name of the radiolabeled drug/compound	**18F-Florbetapir (AmyvidTM)**
Manufacturer and other Information	PETNET Solutions, Inc. Knoxville, TN 37932
Approval Status (select one)	IND application is pending

	IND is approved RDRC approval is pending RDRC is approved **No FDA/RDRC approval is required – Explain** **Amyvid™ (Florbetapir F 18 Injection) is FDA-approved for Use in Patients Being Evaluated for Alzheimer's Disease and Other Causes of Cognitive Decline. In this study, the Florbetapir scan is used to determine if the patient has Alzheimer's biomarker positivity (positive scan) as an inclusion criterion and this is consistent with the FDA-approved indication. For clinical purposes, the result of this PET scan is discussed with the patient at study entry.**
IND #	**N/A**
Who holds the IND (i.e., IND Sponsor). If other than PI/CU Investigator, type name of holder.	**N/A**

Research Related Delay to Treatment

Research involving participants who are in need of treatment invariably involves delay to care, and this delay is associated with risk. Scheduling of procedures must be carefully organized to minimize delay. Other delay must involve only that minimally necessary to accomplish the aims of the research while respecting subject well- being and safety. Describe the delay, by virtue of research participation in this study, before a participant can receive treatment of known efficacy or standard care routinely offered in the community.

Will research procedures result in a delay to treatment? **Yes ☐ No ☒**

Maximum duration of delay to any treatment

The maximum delay between screening and randomization is 6 weeks, during which the patient may be treated with valacyclovir or placebo.

Maximum duration of delay to standard care or treatment of known efficacy

If already prescribed, patients are permitted to receive cholinesterase inhibitors and/or memantine throughout the duration of the study: doses of these medications must be stable for 1 month prior to study entry. It is expected that there will be no changes to either cholinesterase inhibitor or memantine dose during the trial, but if there are clinical changes including side effects to these medications, dose adjustment can be made. In such cases, the change is documented for analytic purposes, e.g., potential analysis as a covariate**.** However, it is unlikely for patients to be taking cholinesterase inhibitors and/or memantine, as these are only FDA-approved medications for Alzheimer's disease, not MCI.

It is even more unlikely that a new prescription for either a cholinesterase inhibitor or memantine will be started in this MCI sample following enrollment, but if it does occur, we will document the change for data analytic purposes.

Patients who experience any of these changes will be permitted to continue study participation.

Psychotropic and other medications will be permitted. Medication dosage of psychotropics may be changed during the trial if indicated by the patient's physician. All medication changes will be documented in the patient's study chart.

Treatment to be provided at the end of the study

All patients are required to have a primary care physician or outside medical provider who manages their clinical treatment and non-study related prescriptions throughout the duration of the study.

After the study ends, the patient will continue to be followed by the physician who was following the patient prior to the start of the study (i.e. referring physician or primary care provider), and may continue valacyclovir or use alternative medications, as clinically indicated.

Clinical Treatment Alternatives

Describe what other treatment or assessment options are available to subjects who do not participate in research.

Commonly used FDA-approved medications for patients with Alzheimer's disease include cholinesterase inhibitors and memantine. They are occasionally prescribed off-label for MCI. Patients can continue on cholinesterase inhibitors and/or memantine, if doses are stable for 1 month prior to study entry. Medication dosage may be changed if indicated by study physician.

Risks/Discomforts/Inconveniences

"Risk" is a broad term used to convey the potential for harm, burden, and inconvenience related to research participation. Use this section to provide a comprehensive description of foreseeable physical, psychological, social, interpersonal, and economic risks introduced by the research. Include the source of the information. Consider both the probability and magnitude of harm and its impact. Describe the foreseeable harms associated with the research (untoward effects of a medication) and those related to delay to individualized treatment. Include data from the literature, and local data, if available, on risk rates and subject experiences with research procedures. Describe procedures in place to minimize risk. In general, please create a numbered list of risks/categories of risk, and in general put the list in the order of significance or level of risk, the most significant risks should be listed first.

In Person Visits and Procedures: During assessments and procedures completed on site, all institutional guidelines and procedures will be followed and implemented by the study team, and adhered to by participants. Any staff or participant unwilling to abide by these guidelines will not be permitted to participate in, or complete work at the study visit.

Valacyclovir Treatment: Patients will come for detailed evaluation at the screening and baseline visits and will continue to receive all medical treatment as needed throughout the 52-week study. Valacyclovir is not FDA- approved for the treatment of amnestic MCI (eMCI or lMCI), but it is FDA-approved for the treatment of HSV1 and HSV2 (and varicella zoster).

If already prescribed, patients are permitted to receive cholinesterase inhibitors and/or memantine throughout the duration of the study: doses of these medications must be stable for 1 month prior to study entry. It is expected that there will be no changes to either cholinesterase inhibitor or memantine dose during the trial, but if there are clinical changes including side effects to these medications, dose adjustment can be made. In such cases, the change is documented for analytic purposes, e.g., potential analysis as a covariate.

It is even more unlikely that a new prescription for either a cholinesterase inhibitor or memantine will be started in this MCI sample following enrollment, but if it does occur, we will document the change for data analytic purposes.

Patients who experience any of these changes will be permitted to continue study participation.

Psychotropic and other medications will be permitted. Medication dosage of psychotropics may be changed during the trial if indicated by the patient's physician. All medication changes will be documented in the patient's study chart.

Common Side Effects: headache 14% drug versus 10% placebo, dizziness 2% drug versus 1% placebo in the largest placebo-controlled trial (n=609). Hallucinations, delirium and seizures occur in less than 1% of patients taking 2-4 g daily, and only in patients with renal failure. Valacyclovir at a high dose of 8 g daily in HIV led to SAEs in 10% of patients. Valacyclovir 3 g daily was efficacious in a randomized, double-blind, placebo-controlled, 18-week trial in 24 patients with schizophrenia with positive HSV1 titers, valacyclovir 3 g/day was superior to placebo with effect sizes of 0.79, 0.97 and 1.14 for tests of working memory, verbal memory, and visual object memory, respectively, from the computerized Penn battery (Prasad et al. 2013). Given the difficulty with achieving efficacy in MCI, we chose 4 g daily to ensure that we do not underdose while avoiding known toxicity associated with much higher doses. In our ongoing VALAD trial that targets a dose of 4 g daily, 2 of 76 patients have discontinued because of putative side effects (double-blind maintained, so they may be on drug or placebo), and 3 of 76 patients have continued at a lower dose of 2 or 3 g valacyclovir/placebo daily (2 g or higher is permitted). It is not uncommon for medical illness to lead to interruption of treatment, usually for short intervals (e.g., surgery). During the study, interruption of treatment with a visit delay for up to 6 weeks will be permitted. Treatment and data collection will resume after the interruption and the patient will continue in the protocol. All serious adverse events will be reported to our IRB and the DSMB.

Neuropsychological Assessment: During neuropsychological testing, some subjects may find some questions upsetting. The tester will discuss the situation with the patient and will allow for an expanded break between tests when feasible. If the patient still chooses not to proceed with testing, the patient's choice will be respected.

UPSIT (Olfaction Assessment): The UPSIT (scratch-and-sniff odor identification test) has been administered to several hundred thousand subjects around the world and its use is not associated with any known side effects. The UPSIT comprises mainly synthetic odors and there is essentially no risk of an allergic reaction with this procedure. If there is an acute upper respiratory infection, testing will be delayed until the participant has recovered.

Remote Assessments: Select subject neuropsychological testing may be administered remotely throughout protocol participation, as described in previous section of PSF. All other study procedures (MRI, PET scan, physical exam) and assessments (majority of subject neuropsychological testing) must be completed in person, on site.

With completion of remote assessments also comes the risk for loss of confidentiality. Remote assessments will be administered exclusively through the HIPAA compliant phone calls at a time agreed upon by both the subject and member of the study team. The individual completing the remote assessments will do so by completing tests and/or interviews verbally, and recording replies on paper CRF, for later storage in the subject chart.

Blood Draws: The risks associated with blood draws include local tenderness, redness, bruising at the puncture site and infection. Also, a feeling of lightheadedness may occur. To help alleviate these risks, only phlebotomy-certified members of the research team will be permitted to collect blood samples from patients.

Apolipoprotein E genotyping: In the Informed Consent form, we will state (1) the presence of specific subtypes of apolipoprotein may be associated with an increased risk of memory disorders, but this is not established, (2) the results will be kept strictly confidential and not released to the subject or to other parties. This approach, required by our IRB for all apolipoprotein genotyping studies, follows from the current ambiguities for clinical application of apolipoprotein E genotyping. Further, given that this involves genotyping, as per our NYSPI/Columbia IRB requirements, we obtained a Certificate of Confidentiality from the NIA, as we have done in other studies. The genotypes are determined blind to subject status (randomized to valacyclovir or placebo) by the sizes of DNA fragments present. No cell lines will be created. Samples can be retracted at the subject's request. No commercial use is intended.

MRI: Subjects will be screened carefully for contraindications to MRI (e.g., metal implants) with a standard Radiology rating form, and excluded from the study if necessary. Subjects with pacemakers or metal implants are excluded from the MRI component of the protocol. In the consent form, subjects are also informed that some people with claustrophobia cannot tolerate being in the MRI scanner. Based on the subject's request, or the judgment of the clinician, subjects at risk of experiencing a claustrophobic reaction are given low dose benzodiazepine (lorazepam 0.5 mg orally) half an hour before the MRI procedure begins (an escort to take the subject home post-MRI is required in such cases). If claustrophobia or anxiety occurs during the procedure, the subject is withdrawn from the scanner between each MRI sequence to improve tolerability. The procedures are then continued if the subject finds it tolerable to continue with the help of these breaks between sequences. For subjects who still cannot tolerate the procedure, the MRI acquisition is terminated.

All subjects will have a radiologist's reading of the MRI scan at Baseline and at 52 weeks. Any significant abnormality will be communicated by the radiologist to the Principal Investigator (Dr. Devanand), who will take appropriate clinical action as needed.

Risks associated with PET in this study are related to A) discomfort during scanning; **B)** radiation exposure; **C)** toxicology (idiosyncratic reaction to the tracer); **D)** pregnancy.

A. Discomfort during scanning: It may be uncomfortable to lie motionless for an extended period of time and it may cause some subjects to feel anxious. Our staff will be available to provide support, reduce anxiety, optimize the comfort of the subject and remove the subject from the machine if requested. In addition to a physician being available, a research assistant who knows the subject will be available to reassure the subject, if needed, in the PET suite.

B. Radiation exposure: Study staff (i.e. Principal Investigator, Study Physician) discussion with potential subjects at Screening documenting inquiry about radiation history, X-rays and other radiological procedures, radiation therapy, and prior research

procedures involving radiation exposure is completed to ensure that the FDA guidelines for annual radiation exposure will not be exceeded when the PET procedures are conducted. Subjects exposed to radiation in the workplace are excluded. If there is any history of additional radiation exposure in the past year; it will be reviewed with PET Center staff for their approval before proceeding.

The total radiation exposure from 18F-Florbetapir (370 MBq; 10 mCi per scan) with two scans done one year apart from each other falls well within FDA guidelines on allowable radiation exposure.

Total effective (radiation) dose per one administration of 18F-Florbetapir is 7.03 mSv and 2.35 mSv from one diagnostic head CT scan.

Subjects will be encouraged to drink fluids and to void, which will help ameliorate the bladder dose (of 18F- Florbetapir).

C. Toxicology of 18F-Florbetapir: There are no known somatic adverse effects resulting from exposure to either of this tracer.

The Gallbladder is the limiting organ for 18F-Florbetapir. For 1, 18F-Florbetapir scan (Dose 10 mCi) the absorbed dose (Gallbladder Wall) is 52.91 mGy.

The Florbetapir absorbed dose was approved by the JRSC at the dose as administered in this protocol, because the limits set forth in CFR 21 361.1 do not apply to this protocol.

D. Pregnancy:

Studies involving radiation are contraindicated during pregnancy because of possible risk to the fetus. This study will only enroll post-menopausal women as determined by a patient report of 12 consecutive months without menstruation.

Upon learning of a positive result to Amyloid PET scan, patients may become upset. A Study Physician will answer any questions or concerns patients may have regarding amyloid PET imaging and results.

Radiation Dosimetry:

Table 1: Florbetapir Dose 10 mCi

a. Gastrointestinal (See full dosimetry table; pending as of 10/21/2020).

b. Assumed radiation weighting factor wr (formerly defined as quality factor, Q) of 1 for conversion of absorbed dose (Gray or rads) to dose equivalent (Sieverts or rem) for F 18. To obtain radiation absorbed dose in rad/mCi from above table, multiply the dose in µGy/MBq by 0.0037, (e.g., 14 µGy/MBq x 0.0037 = 0.0518 rad/mCi)

The effective dose resulting from a 370 MBq (10 mCi) dose of Amyvid is 7.03 mSv in an adult, (19 x 370 - 7030 µSv = 7.030 mSv). The use of a CT scan to calculate attenuation correction for reconstruction of Amyvid images (as done in PET/CT imaging) will add radiation exposure. Diagnostic head CT scans using helical scanners administer an average of 2.2 +/- 1.3 mSv effective dose (CRCPD Publication E-07-2, 2007). The actual radiation dose is operator and scanner dependent.

The total radiation exposure from Amyvid administration and subsequent scan on a PET/CT scanner is estimated to be 9.38 mSv per 1 scan. The total effective dose for study/protocol from 18F-Florbetapir is 14.06 mSv (accounting for screening or baseline and week 52 scanning).

The total radiation exposure from both tracer and scan on a PET/CT scanner is estimated to be 18.76 mSv, accounting for Amyloid PET scan completed at Screening or baseline and Week 52. The additional cancer risk from this research study is estimated to be up to 0.13%. At these low levels, scientists are uncertain as to the actual risk and there may be no risk at all. The risk estimate is based on the subjects in the study population who are most sensitive to radiation exposure.

Additional tables for reference: see JRSC Final Datasheet (see in "Uploads" section of PRISM). Describe procedures for minimizing risks

There are three areas in which safeguards to protect subjects from undue risk require discussion. These include the procedures used to obtain informed consent, the procedures used to ensure confidentiality of subjects' responses and findings on tests, and the procedures used to minimize possible risks associated with the research procedures.

Informed Consent: Informed consent is obtained and documented with a signed consent statement giving full information about the study. In the consent form and in discussion with an investigator, subjects are advised fully of the procedures to be used, the amount of time required of them, the fact that this is a longitudinal treatment study with repeated assessment at specified time points, the possible risks and benefits of the procedures and the treatment conditions, their right to refuse participation in the study without prejudice, their right to terminate participation at any moment without prejudice, and the name and telephone number of the Principal Investigator. All informants will be required to sign the "Informant Information Sheet" to indicate that they agree to the responsibilities detailed in the document.

Capacity to Consent: Based on IRB requirements, patients will be recruited by a study physician who signs the consent form in addition to the patient. As described earlier, for patients who lack the capacity to consent but retain the capacity to appoint a surrogate, we will follow the procedures required by the NYSPI IRB (based on New York State OMH regulations) regarding assessment of capacity to consent.

Research Procedures: We have described above the potential risks of the research procedures and the safeguards that will be used to minimize risks. These include termination of subjects from research participation if it is believed that such participation endangers their welfare. Monitoring procedures are used to evaluate potential side effects of research procedures. The protocol stipulates an extensive medical, neurological, and psychiatric evaluation of all subjects as a condition for research participation.

Methods to Protect Confidentiality

Describe the data management plan and the methods you will employ to protect subject privacy and the confidentiality of research data. The section should detail how information will be collected, recorded, coded, stored, transmitted, and as applicable, shared with other investigators so as to minimize risks related to breach of confidentiality. Confirm that identifiers are removed, to the extent possible, from research data, and explain if there are links between subject identity and research data, or if the data are anonymous. Also, indicate where the data are stored, who is responsible for data safekeeping, and who has access to subject identity and codes, if any, which cross-link research data and subject identity.

Confirm that identifiable data are not collected, stored, or transmitted by mail, fax, on removable drives, laptops, or via the internet without proper protections, e.g. encryption.

Confidentiality of Subjects' Responses. In the informed consent form, subjects are told that the information they provide, and all findings will be kept strictly confidential, with access limited to the research staff with the possible exception of State or Federal regulatory personnel for audits. All records are kept in locked files. Each subject is given a code number for database purposes, and the patient's name does not reside in the database. Computer files will be stored in a database that is password protected and behind an institute and department firewall. No one but the project staff has access to the master list linking subjects' names to code numbers, and all information obtained is coded. The master list is kept under strict lock and key. The research data on specific measures are released to the patients, and this is specified in the consent form. This research will be covered by a Certificate of Confidentiality (CoC) from the NIH.

Will the study be conducted under a certificate of confidentiality?

☐ Yes, we will apply for the Certificate of Confidentiality

☒ **Yes, we have already received a Certificate of Confidentiality**

☐ No

Direct Benefits to Subjects

Describe only benefits to individual subjects that are likely to accrue during the study itself. Do not include subject compensation or treatment to be provided at the end of the study, as these do not figure into the IRB's risk/benefit considerations. Do not describe diagnostic and evaluation components unless subjects receive clinical feedback. Do not describe the anticipated scientific benefits of the research. Some studies offer no direct benefit to subjects.

The study was not designed for the direct benefit of participants. Potential benefits to society may be considerable. If the hypotheses are supported by the results, this will suggest that valacyclovir may be a useful treatment for amnestic MCI (eMCI or lMCI) in AD Biomarker positive patients, who are serum antibody positive for HSV1 or HSV2.

Compensation and/or Reimbursement

If compensation or reimbursement for expenses will be offered to subjects, please describe and indicate total amount and schedule of payment(s). If transportation is reimbursed, state if receipts are necessary for reimbursement. Include justification for compensation amounts and indicate if there are bonus payments.

Each patient will be paid:

For Screening or Baseline Amyloid PET: $100.00 For Week 52 Amyloid PET: $100.00

For Baseline MRI: $50.00 For Week 52 MRI: $50.00

For each of 5 study visits: $50.00 at each time-point.

Transportation Costs are estimated at $100.00 per patient, for 52 weeks of protocol participation though $100.00 is not an absolute cut off. Transportation expenses exceeding $100.00 will be reimbursed by the study team, provided that receipts are procured by participants and given to members of the study team for verification and reimbursement processing.

Payments will be made using petty cash, which will be provided to participants at the end of each visit and/or procedure. Total payment for completion of all sessions (including transportation) could total $650.00.

Data Management Plan

All federally funded, more than minimal risk studies are required to include a Data Management Plan. The required elements of the Data Management Plan include: identification of the database platform (e.g., REDCap) and inclusion of an attestation that it is Part 11 compliant, identification of a qualified staff member who designs and maintains the database, design and implementation of data system training for all Principal Investigators & research coordinators & all protocol staff, and significant changes to the data management plan will be submitted as protocol amendments in PRISM. More information can be found on the IRB website at https://irb.nyspi.org/forms regarding this plan and should be reviewed prior to submission.

All federally funded, more than minimal risk studies are required to include a Data Management Plan. The required elements of the Data Management Plan include: identification of the database platform (e.g., REDCap) and inclusion of an attestation that it is Part 11 compliant, identification of a qualified staff member who designs and maintains the database, design and implementation of data system training for all Principal Investigators & research coordinators & all protocol staff, and significant changes to the data management plan will be submitted as protocol amendments in PRISM. More information can be found on the IRB website at https://irb.nyspi.org/forms regarding this plan and should be reviewed prior to submission.

All research data in this protocol is collected on paper forms and entered into a REDCap project designed by the NYSPI Data Coordinating Center (DCC) in consultation with Dr. Devanand and his staff and all forms are developed in REDCap by DCC staff (Mental Health Data Science Division) under the supervision of DCC director Dr. Howard Andrews. An online Data Access Request form must be submitted for each staff member to access the system, and approved by Dr. Devanand. Each authorized user receives his own login credentials, and all data in the REDCap system is associated with that individual in the REDCap audit trail. The DCC monitors user access periodically to ensure ongoing approval of each authorized individual. The audit system documents all changes made to individual data fields, including original value, modified value, date of modification and identity of the individual making the change. All variables in the REDCap system have associated labels documenting the content of the data field, and all numeric categorical variables have associated labels documenting the meaning of each value. For statistical analysis, reporting and quality assurance checks, data are exported into SPSS or SAS files including all documentation, or Excel files with codebook information. Each data export must be approved by Dr. Devanand, and data are transmitted to the authorized recipient via NYSPI's secure ftp application (attached). Until all data collection is completed and the database is locked, data with treatment assignments required for unblinded analysis are shared only with the Data Safety and Monitoring Board.

It is important to note that all information collected in compliance with regulatory requirements (maintained in the 'regulatory binder') is captured on paper forms, with 'wet' signatures; these paper-based forms include HIPAA consent and subject consent for participation in the project. More specifically, all source documentation, including regulatory documents, are in paper form; there is no reliance in #8089 on the REDCap electronic system for source documentation and REDCap's electronic signature functionality is not required for this project since all required signatures are in 'wet' form, on paper. And while the DCC's REDCap system is CFR 21 Part 11 compliant (please see attached checklist), many of these items are not applicable to the REDCap data capture system since none of the data captured in REDCap represents a source document. Data entered into the REDCap project is checked for accuracy against source documentation.

References

Please limit references, preferably no more than twenty.

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Uploads

-Bolded Consent Form(s)-
BOLDED_8089_CONSENT_11.13.23.pdf
BOLDED_8089_CONSENT_PROCEDURE_NOTE_11.13.23.pdf
-Miscellaneous Document(s)-
DevanandDavangere_ADDF_Application_2.26.2020_v1-2.pdf
8089.MRIFindingsLetter.No Findings_2023pdf.pdf
8089.MRIFindingsLetter.Significance_2023pdf.pdf
-Certificate of Confidentiality-
Certificate of Confidentiality.pdf
-FDA IND Approval(s)-
05272021_VALMCI_IND.pdf
8089_IND_Decision_Worksheet.pdf
-JRSC Approval(s)-
JRSC IRB 8089 APH-AABL9451 appr letter 11-30-2020md.pdf
-Bolded Information Sheet(s)-
BOLDED_8089_CF_SUMMARY_11.13.23.pdf
-Miscellaneous Document(s)-
8089.MRIFindingsLetter.Uncertain Significance_2023.pdf
MRI Updates_Consent Form Guidance.pdf
TO_BE_APPROVED_8089_PHONE_SCREEN_SCRIPT_11.13.23.pdf
CHRISTOPHER_STANLEY_DMP_APPROVAL.pdf
8089_BOLDED_PSF_11.24.23.pdf
UNBOLDED_IE_CONFIRMATION_11.16.23.pdf
BOLDED_IE_CONFIRMATION_11.16.23.pdf
SRMP_Checklist 11.24.23.pdf
-Unbolded Consent Form(s)-
TO_BE_STAMPED_8089_CONSENT_11.13.23.pdf
TO_BE_STAMPED_8089_CONSENT_PROCEDURE_NOTE_11.13.23.pdf
-Unbolded Information Sheet(s)-
TO_BE_STAMPED_8089_CF_SUMMARY_11.13.23.pdf
-Unbolded Assent Form(s)-
NYSPI_8089_Unstamped_PCS_10 06 2023_English Spanish.pdf
-HIPAA Form(s)-
To Be Stamped_8089_HIPAA_10 06 2023_English.pdf