Neurodegenerative Alzheimer's Disease and Amyotrophic Lateral Sclerosis (NADALS) Basket Proof of Concept Trial including Asymptomatic Individuals using Baricitinib

Regulatory Sponsor:	Mark Albers, MD, PhD
Funding Sponsor:	Philanthropy
Study Product:	Baricitinib
Protocol Short Title:	NADALS Basket Trial
IND Number:	154641 154642
Version Number:	10.0

29April2024

STATEMENT OF COMPLIANCE

This study will be conducted in compliance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP), and the applicable regulatory requirements under United States Code of Federal Regulations (CFR) Title 45 CFR Part 46 and Title 21 CFR Parts 50, 56, and 312.

SIGNATURE PAGE

I have read the attached protocol entitled, "**Neurodegenerative Alzheimer's Disease and Amyotrophic Lateral Sclerosis (NADALS) Basket Proof of Concept Trial including Asymptomatic Individuals using Baricitinib**" dated **29April2024** (**Version 10.0**) and agree to abide by all described protocol procedures. I agree to comply with the International Council for Harmonisation Guideline on Good Clinical Practice, applicable FDA regulations and guidelines identified in 21 CFR Parts 11, 50, 54, and 312, local Institutional Review Board (IRB) guidelines and policies, and the Health Insurance Portability and Accountability Act (HIPAA).

Site Investigator: _____

Signed: _____ Date: _____

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LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
ADR	Adverse Drug Reactions
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
AE	Adverse Event/Adverse Experience
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	Amyotrophic Lateral Sclerosis Functional Rating Scale Revised
ALT	Alanine transaminase
AROMHA	Accessible Remote Olfactory Mediated Health Assessments
AST	Alanine aminotransferase
CBC	Complete Blood Count
CC	Coordination Center
CCL2	Chemokine Ligand 2
CFR	Code of Federal Regulations
CIB	Clinical Investigator's Brochure
sIRB	Single Institutional Review Board
CLIA	Clinical Laboratory Improvement Amendments
CRF	Case Report Form
CSF	Cerebrospinal Fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CXCL10	C-X-C Motif Chemokine Ligand 10
DM	Data Management
DMARD	Disease-modifying antirheumatic drug
DPS	Diaphragm Pacing System
DSMB	Data and Safety Monitoring Board
dsRNA	Double-stranded RNA
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FSV	Final Safety Visit
FWA	Federal-wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFNG	Interferon Gamma
IL-6	Interleukin 6
IND	Investigational New Drug Application
IRB	Institutional Review Board

JAK	Janus Kinase
LP	Lumbar Puncture
MCI	Mild Cognitive Impairment
MCP1	Monocyte Chemoattractant Protein 1
MGH	Massachusetts General Hospital
MoCA	Montreal Cognitive Assessment
MOP	Manual of Procedures
NfL	Neurofilament Light Chain
NIH	National Institutes of Health
NPI-Q	Neuropsychiatry Inventory Questionnaire
OAT3	Organic Anion Transporter 3
PAV	Permanent Assisted Ventilation
PD	Pharmacodynamics
PE	Pulmonary Embolism
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetics
PKR	Protein Kinase R
pPKR	Phospho-protein Kinase R
POEM	Percepts of Odor Episodic Memory
QA	Quality Assurance
QC	Quality Control
RZV	Recombinant Zoster Vaccine
SAE	Serious Adverse Event/Serious Adverse Experience
SCD	Subjective Cognitive Decline
SI	Site Investigator
SOP	Standard Operating Procedure
SVC	Slow Vital Capacity
TB	Tuberculosis
TBL	Total Bilirubin
TDP-43	TAR DNA-binding Protein 43
ULN	Upper Limit of Normal
US	United States
WOCBP	Woman of Childbearing Potential

PROTOCOL SUMMARY

Study Title
Neurodegenerative Alzheimer's Disease and Amyotrophic Lateral Sclerosis (NADALS) Basket Proof of Concept Trial including Asymptomatic Individuals using Baricitinib

Version Number
10.0

Study Indication
Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and asymptomatic carriers of an ALS-causative gene

Phase of Development
Phase II

Rationale for the Study
Converging evidence reveals Type I interferon signaling is robustly active within the central nervous system of subsets of patients with AD and ALS, both in autopsied brains and profiles of cerebrospinal fluid (CSF) of living patients. In animal models, activation of type I interferon signaling leads to propagated neurodegeneration within a neural circuit. In cultured human neurons, activation of type I interferon signaling results in neuronal death within 48 hours. Baricitinib, a drug that blocks type I interferon signaling, also protects cultured human neurons from death. We have characterized a signature of type I interferon signaling in the brains and CSFs of AD and ALS patients as a biomarker signature for this inflammatory mechanism of neuronal death.

This proof of concept trial will ascertain whether baricitinib at 2 mg per day, 4 mg per day, or both reaches therapeutic levels in the CSF and suppresses inflammatory markers associated with type I interferon signaling among AD and ALS patients with evidence of abnormal type I interferon signaling at baseline.

Study Design
This is an open-label, biomarker-driven basket trial of baricitinib in people with AD, ALS, or asymptomatic carriers of an ALS causative gene, such as a hexanucleotide expansion in the *C9ORF72* gene. Baricitinib is approved by the FDA in the United States (US) for rheumatoid arthritis at 2 mg per day and for alopecia and COVID-19 at both 2 mg and 4 mg per day.

Each participant will be treated with open-label baricitinib for 24 weeks. Participants will receive baricitinib 2 mg per day by mouth for the first 8 weeks and baricitinib 4 mg per day by mouth for the remaining 16 weeks. Participants will have a lumbar puncture (LP) at screening and CSF will be examined for study eligibility. Participants will be enrolled if their CSF level of chemokine ligand 2 (CCL2; also known as monocyte chemoattractant protein 1 (MCP1)) is 250 pg/mL or greater and if they meet all other eligibility criteria(1-2). All enrolled participants must have received a first dose of recombinant zoster vaccine (RZV; also known as Shingrix) within 4 years prior to treatment initiation.

Blood and urine will be collected and a second LP will be performed to collect CSF prior to dosing at the Baseline Visit. Safety labs will be assessed in blood and urine. Biomarkers of inflammation and neuronal

death will be measured in plasma and CSF. DNA will be extracted from whole blood. One week after starting baricitinib 2 mg per day, blood will be drawn for a complete blood count (CBC) to rule out leukopenia. Blood will be drawn and a third LP will be performed two to four hours after dosing during the Week 8 Visit to measure study drug levels and biomarkers of inflammation and neuronal death. Blood and urine will be collected for safety labs. After the Week 8 Visit, participants will start barticitinib 4 mg per day. One week after starting barticitinib 4 mg per day, a safety visit will be conducted. Blood will be drawn and a fourth LP performed two to four hours after dosing during the Week 16 Visit to measure study drug levels and biomarkers of inflammation and neuronal death. Blood and urine will be collected for safety labs. Participants will continue on baricitinib until Week 24. After 24 weeks, a visit will be conducted to collect clinical outcomes as well as safety and research labs.

On an approximately monthly basis after the first participant completes Week 8, interim analyses will be conducted to assess pharmacokinetic (PK) and pharmacodynamic (PD) markers in the CSF. Interim analyses will be conducted until at least one participant meets the continuation criterion of PK or PD response. No additional interim analyses will be conducted once one participant is found to meet the continuation criterion. Enrollment will be suspended after 10 participants enroll if no participant has yet met the continuation criterion, including no fewer than 2 AD, MCI, or SCD participants and no fewer than 2 ALS participants (of whom no more than 1 may be an asymptomatic carrier of an ALS-causative gene). Enrollment will be terminated if the continuation criterion has not been met after 10 participants complete their full protocol.

Study Objectives

The primary objectives of the study are:

- To assess whether 8 weeks of an oral dosage of baricitinib 2 mg per day, 4 mg per day, or both achieves measurable levels of baricitinib in the CSF of patients with AD, ALS, and asymptomatic carriers of an ALS-causative gene.
- To determine whether 8 weeks of an oral dosage of baricitinib 2 mg per day, 4 mg per day, or both decreases levels of the inflammatory biomarker CCL2 in the CSF of patients with AD, ALS, and asymptomatic carriers of an ALS-causative gene.

The secondary objectives of the study are:

- To determine whether 8 weeks of an oral dosage of baricitinib 2 mg per day, 4 mg per day, or both decreases levels of the inflammatory biomarkers interleukin-6 (IL-6), phospho-protein kinase R (pPKR), PKR, pPKR / PKR ratio, C-X-C motif chemokine ligand 10 (CXCL10), or interferon gamma (IFNG) in the CSF of patients with AD, ALS, and asymptomatic carriers of an ALS-causative gene.
- To determine whether 8 weeks of an oral dosage of baricitinib 2 mg per day, 4 mg per day, or both decreases levels of the neuronal death biomarkers neurofilament light chain (NfL), tau, or phospho-tau in CSF or TAR DNA-binding protein 43 (TDP-43) levels in the plasma in patients with AD, ALS, and asymptomatic carriers of an ALS-causative gene.
- To determine whether the measured concentration of baricitinib in the CSF or blood (pharmacokinetics) after 8 weeks of an oral dosage of baricitinib 2 mg per day, 4 mg per day, or both correlates with the changes in CSF biomarkers (pharmacodynamics).

- To determine whether 8 weeks of an oral dosage of baricitinib 2 mg per day, 4 mg per day, or both is safe and tolerable in patients with AD, ALS, and asymptomatic carriers of an ALS-causative gene.

The exploratory objectives of the study are:

- To determine whether 8 weeks of an oral dosage of baricitinib 2 mg per day, 8 weeks or 16 weeks of baricitinib 4 mg per day, or both decreases levels of the inflammatory biomarkers CCL2, IL-6, pPKR, PKR, pPKR / PKR ratio, CXCL10, or IFNG in the plasma of patients with AD, ALS, and asymptomatic carriers of an ALS-causative gene.
- To determine whether changes in clinical outcomes correlate with CSF drug concentration or with changes in CSF biomarkers after 8 weeks of an oral dosage of baricitinib 2 mg per day, 4 mg per day, or both.
- To collect CSF for further biomarker discovery efforts via proteomics, dsRNA-seq, and other unbiased chemical profiling methods.
- To refine the CSF inflammatory signature for AD and ALS patients and identify factors that predict diminishment of the CSF inflammatory signature after 8 weeks of an oral dosage of baricitinib 2 mg per day, 4 mg per day, or both.

Study Endpoints

The primary outcome measures for the study are:

- Level of free baricitinib in the CSF.
- Change in levels of the inflammatory biomarker CCL2 in the CSF (from baseline to 8-weeks and to 16-weeks).

The secondary outcome measures for the study are:

- Changes in the inflammatory biomarkers pPKR, PKR, pPKR/PKR ratio, CXCL10, and IFNG in the CSF (from baseline to 8-weeks and to 16-weeks).
- Changes in the neuronal death biomarkers NfL, tau, and phospho-tau in the CSF and TDP-43 in plasma (from baseline to 8-weeks and to 16-weeks).
- Association between drug concentration (pharmacokinetics) and CSF biomarkers (pharmacodynamics).
- Treatment-emergent adverse events.
- Permanent discontinuation of study drug due to study drug-related AEs.

The exploratory outcome measures for the study include:

- Changes in the inflammatory biomarkers IL-6, CCL2, pPKR, PKR, pPKR/PKR ratio, CXCL10, and IFNG in plasma (from baseline to 8-weeks, to 16-weeks, and to 24-weeks).
- Changes in clinical outcomes (from baseline to 24-weeks) relative to previous trajectories, when available.
- Change in Accessible Remote Olfactory Mediated Health Assessments (AROMHA) olfactory battery score.

Study Locations
Up to two centers in the United States will participate in the study.

Number of Planned Participants
20 participants (10 AD and 10 ALS or asymptomatic carriers of an ALS-causative mutation, with a limit of 5 asymptomatic carriers).

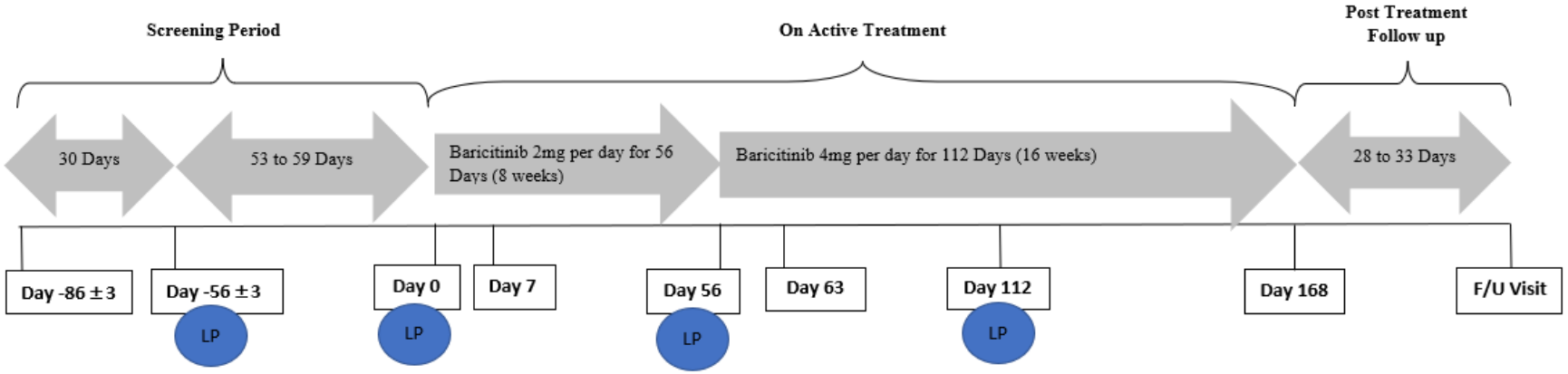
Study Population
AD patients: This study will be conducted in participants who have subjective cognitive decline, mild neurocognitive disorder, or major neurocognitive disorder, either possible or probable AD. Eligible participants must be between 55 and 90 years old, inclusive, and have a MoCA score ≥ 8 at screening. Participants or a surrogate representative must provide written informed consent prior to screening. A study partner must be willing to accompany the participant to visits and complete partner study forms. All participants must be able and willing to undergo LPs. Detailed criteria are described in the body of the protocol.

ALS patients: This study will be conducted in participants who meet the El Escorial criteria of possible, laboratory-supported probable, probable, or definite criteria for a diagnosis of ALS. Asymptomatic individuals with an ALS-causative gene per CLIA-certified genetic testing results are also eligible to participate in this study at MGH. Participants must provide written informed consent prior to screening. Eligible participants must be between 18 and 80 years old, inclusive, have an ALSFRS-R score ≥ 27, and be ambulatory at screening. Participants not taking or on a stable dose of any FDA approved treatment for ALS for at least 30 days or 1 cycle and women of child-bearing age at screening are eligible for inclusion as long as they meet specific protocol requirements. All participants must be able and willing to undergo LPs. Detailed criteria are described in the body of the protocol.

Treatment Groups
Open-label baricitinib 2 mg per day for 8 weeks, followed by baricitinib 4 mg per day for 16 weeks.

Duration of Treatment and Follow-up
Participants will remain on treatment for 24 weeks. Participants who withdraw consent or early terminate from the study will be asked to complete a Final Safety Visit when they notify the site of their desire to end participation or as soon as possible thereafter. All participants will be asked to complete a Follow-up Telephone Call 28 to 33 days after their last dose of study drug.

STUDY WORKFLOW



Participants who withdraw consent or early terminate from the study will be asked to complete a Final Safety Visit. All participants will be asked to complete a Follow Up Telephone Call 28 to 33 days after taking their last dose of study drug.

LP = Lumbar Puncture (LP) at Visit

SCHEDULE OF ACTIVITIES

ACTIVITY	Screening Visit	Study Drug Administration						Follow-Up Telephone Call[15]
		Baseline Visit	Week 1	Week 8	Week 9	Week 16	Week 24/Final Safety Visit[14]	
	Visit 1[1]	Visit 2[1]	Visit 3[16]	Visit 4	Visit 5[16]	Visit 6	Visit 7	Visit 8
	Clinic	Clinic	Remote or Clinic	Clinic	Remote or Clinic	Clinic	Clinic	Phone
Visit Window	See Footnote 1	Day 0	Day 7 ±2	Day 56 -4 or +1	Day 63 +2	Day 112 ±4	Day 168 ±4	28 to 33 days
Written Informed Consent	X							
Eligibility Review	X	X						
Medical History	X							
Demographics	X							
AD/ALS History and Diagnosis History	X							
El Escorial Criteria **(ALS only)**	X							
Recombinant Zoster Vaccine (RZV; Shingrix)[2]	X			X				
Physical Examination	X						X	
Neurological Exam	X						X	
Vital Signs[3] & Weight	X	X	X	X	X	X	X	
Height	X							
12-Lead ECG	X							
ALSFRS-R **(ALS only)**	X	X		X			X	
Slow Vital Capacity (SVC)[4] (**ALS only)**	X	X		X			X	
NIH Toolbox **(Asymptomatic carriers of an ALS-causative gene only)**-MGH site only		X					X	
Neuropsychiatric Inventory Questionnaire (NPI-Q) **(AD only)**		X					X	
ADAS-Cog **(AD only)**		X					X	
Montreal Cognitive Assessment (MoCA) **(AD only)**	X						X	
AROMHA olfactory battery		X					X	

Baseline Columbia-Suicide Severity Rating Scale (C-SSRS)	X							
Since Last Visit C-SSRS		X	X	X	X	X	X	
End of Study Form							X	
Global Impression of Change survey[5]							X	
Survival assessment		X	X	X	X	X	X	
Screening Labs (Blood & Urine)[6]	X							
Safety Labs (Blood & Urine)[7]		X	X	X	X	X	X	
Blood draw for PK analysis[8]		X		X		X	X	
Blood draw for Biomarker Testing and Immune Cell Profiling[9]	X	X		X		X	X	
Blood draw for Genetic Testing[10]		X						
Urine sample for Future Research[11]		X		X		X	X	
Lumbar puncture (LP) and CSF collection[12]	X[17,18]	X[18]		X[18]		X[18]		
Concomitant Medication Review[19]	X	X	X	X	X	X	X	X
Adverse Event Review	X	X	X	X	X	X	X	X
Dispense Study Drug[13]		X		X		X		
Drug Accountability				X		X	X	

[1] Screening Visit activities may be performed over a period of 30 days. The Baseline Visit will occur 53 to 59 days after the Screening LP.
[2] All study participants must receive at least one dose of RZV prior to treatment initiation. The first dose should be administered after all other eligibility criteria have been confirmed and at least 14 days prior to the Baseline Visit unless the participant has provided documentation of vaccination within 4 years prior. The second dose of RZV can be administered at the Week 8 Visit or any time within 2 to 6 months after the first dose per CDC guidelines.
[3] Vital signs include systolic and diastolic pressure in mmHg, respiratory rate/minute, heart rate/minute and temperature. Vital signs will not be collected at remote visits.
[4] SVC testing is required at the Screening Visit and Week 24 or Final Safety Visit but is optional at additional study visits. Every attempt should be made to perform SVC at required visits. SVC or Forced Vital Capacity (FVC) can be performed in a pulmonary function lab, if necessary.
[5] The study participant, study partner (for AD patients only), and investigator will complete a Global Impression of Change survey at the Week 24 or Final Safety Visit.
[6] Screening labs include Hematology (CBC with differential), Comprehensive metabolic panel (including liver function tests), Coagulation, B12, thyroid stimulating hormone(TSH), folate, HIV, Hepatitis B panel, Hepatitis C panel, Urinalysis, and Urine pregnancy test (for WOCBP). Participants will also be tested for Tuberculosis (TB) at the Screening Visit (see Section 8.1.2 Clinical Laboratory Assessments for additional information regarding TB testing).

[7] Safety labs include Hematology (CBC with differential), Comprehensive metabolic panel (including liver function tests), Coagulation, Urinalysis, and Urine pregnancy test (for WOCBP). A Lipid Panel will be collected at the Baseline, Week 8, and Week 24.
[8] All participants will provide a blood sample for PK analysis at the Baseline Visit (pre-dose). At Week 8, Week 16, and Week 24, samples will be collected 1 hour (±10 minutes) post-dose.
[9] All participants will provide a blood sample for biomarker testing and immune cell profiling as well as storage in a biorepository. At Week 8,Week 16 and Week 24, samples will be collected 1 hour (±10 minutes) post-dose.
[10] All participants will provide a blood sample for genetic testing for *C9ORF72* repeat expansion and *APOE* genotype. The sample will be sent to Prevention Genetics for analysis and results will be returned to participants.
[11] Participants will provide a urine sample for storage in a biorepository for use in future research.
[12] CSF will be collected for PK and biomarker analysis. The results of CSF examination from the Screening LP are needed to determine participant eligibility and before the Baseline Visit can occur. The Week 8 and Week 16 LPs will be performed 2 to 4 hours post-dose, ideally 2 hours post-dose.
[13] Administer the first dose of study drug AFTER all Baseline Visit procedures are completed and a final eligibility determination is made. At Week 8, Week 16 and Week 24, participants will bring all remaining study drug to clinic and dose in clinic from home supply at the beginning of the visit. Time of study drug administration will be recorded.
[14] Participants that withdraw consent or early terminate will be asked to complete a Final Safety Visit when they notify the site of their desire to end participation or as soon as possible thereafter.
[15] The Follow-up Telephone Call will be conducted 28 to 33 days after the participant takes their last dose of study drug (regardless of whether or not they have discontinued from the study).
[16] Visits may be conducted in clinic or remotely. Remote visits can occur via telemedicine or telephone with local safety lab collection.
[17] If a patient had a LP and CSF collected within 6 months of the Screening Visit, please contact the Coordination Center to confirm if this CSF sample could be utilized in place of the screening LP. Allowing CSF from a prior LP will be determined on case by case basis.
[18] Review of CBC and Coagulation results is required to confirm if LP can be performed. Please follow local policies for performing LPs and refer to Section 8.1.10 Lumbar Puncture for CSF collection of the protocol.
[19] Routine vaccinations(i.e. influenza, COVID-19, etc.) received during the course of the trial should be administered at least 14 days prior to LP visits and will be recorded on the Concomitant Medication Log. Any live vaccinations are not recommended for participants taking Baricitinib.

1 ETHICS/PROTECTION OF HUMAN PARTICIPANTS

1.1 Institutional Review Board (IRB)

This study will be conducted in compliance with current Good Clinical Practices (GCP) and Title 21 Part 56 of the United States of America Code of Federal Regulations (CFR) relating to IRBs.

1.2 Ethical Conduct of Study

The study will be conducted in accordance with GCP defined by the International Council for Harmonisation (ICH) and the ethical principles of the Declaration of Helsinki.

1.3 Participant Information and Consent

This study will be conducted in compliance with Title 21 Part 50 of the United States of America Code of Federal Regulations (CFR), Federal Regulations and ICH Guidance Documents pertaining to informed consent. At the first visit, prior to initiation of any study-related procedures, an investigator will meet with the potential participant to review and discuss the details of the study using the informed consent document as a guide. This discussion will include all the required elements of informed consent, including the purpose of the research, the procedures to be followed, the risks and discomforts, as well as potential benefits associated with participation, and alternative procedures to study participation. Their questions will be answered to their satisfaction. The participant will be provided with adequate time to reflect on the potential benefits and risks and possible discomforts of participation, and to make an informed decision. Consent will be obtained by a Site Investigator or delegated Sub-Investigator, including physician and licensed Nurse practitioner or Physician Assistant sub-investigators. The Site Investigator or Sub-Investigator will then obtain written informed consent from each participant prior to the initiation of any study procedures. All potential participants will be given the opportunity to speak with the Physician Investigator should a Nurse Practitioner or Physician Assistant be involved in obtaining informed consent.

Informed consent can be obtained remotely according to site's local policies for remote consenting.

1.3.1 Assent

The capacity to consent is gauged by an experienced licensed clinician investigator prior to the consent process through an evaluation of the participant's understanding of their condition, their options for treatment, their understanding of the potential benefits and risks of participating in the clinical trial and of their understanding regarding the voluntary nature of their participation in the trial. In addition, participants are evaluated for their level of orientation and understanding of what will happen during the trial. This process is recorded as part of the consent discussion documentation.

Investigators will continually monitor capacity to understand and consent throughout the study when interacting with the patient at each visit. All study staff will report any changes in function of the participant to the investigators, who will then reassess and document any changes in the patient's capacity to consent.

If a participant is deemed unable to consent, either at the start of the study or while participating in the study, then consent will be obtained from a legally authorized representative. The relationship of the representative to the participant will be documented and kept for our records. The list of eligible legally authorized representatives, in order of preference, is as follows:

1. Court appointed guardian with specific authority to consent to participation in research or authority to make health care decisions for a class of diagnostic and therapeutic decisions inclusive of the proposed research.

2. Health care proxy/person with durable power of attorney with specific authority for making health care decisions inclusive of the proposed research.

3. Spouse, adult child, or adult sibling.

Participants who cannot give informed consent must be able to give assent. If the individual objects to participation, they will not be enrolled. Investigators will document capacity to give assent during the consenting process.

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Many age-associated neurodegenerative diseases, including Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS), are associated with increased inflammatory signaling in the central nervous system. While there is growing evidence that activation of inflammatory signaling leads to neuronal death in cell-based models and leads to signs and symptoms of neurodegeneration in animal models, no disease modifying anti-inflammatory drugs for AD or ALS have been found to date. Recent observational studies of anti-inflammatory drugs used to treat rheumatoid arthritis suggest the potential of these drugs to prevent a diagnosis of AD (3-7). To date, no clinical trials of anti-inflammatory drugs approved to treat rheumatoid arthritis have been performed in patients with ALS or AD. Moreover, the root causes of neuroinflammatory responses in both AD and ALS has been elusive.

Recently, the Albers lab discovered that cytoplasmic double stranded RNA (dsRNA) accumulates in neurons and glia in a subset of cases of AD and ALS (8). It is well established that dsRNA triggers innate immune signaling in a variety of cell types, and indeed, we see activation of interferon signaling in the vicinity of dsRNA in human brains from Alzheimer's and ALS patients. In complementary studies, transgenic mice that express cytoplasmic dsRNA, which is encoded in the genome, exhibit profound neuronal loss that spreads between neural circuits in the brain. Moreover, we find biomarkers of dsRNA activation and interferon signaling in the cerebrospinal fluid (CSF) of a subset of patients with AD and ALS. Baricitinib, an FDA-approved drug for rheumatoid arthritis, rescued inflammatory biomarkers and neural cell death in a human neural cell culture model of dsRNA-mediated interferon induction and death in a dose-dependent manner(9). A recent case report of treatment of a pediatric interferonopathy and progressive neurodegeneration (Aicardi-Goutieres disease) with a structurally related Janus Kinas(JAK) inhibitor, ruxolitinib, resulted in a clinical response with ascension of developmental milestones, reduced inflammatory biomarkers in the CSF, and 5-fold increased blood brain penetration relative to healthy controls reported during the Phase I study (10).

In this trial, we will evaluate the FDA-approved JAK inhibitor baricitinib using an escalating dose design. Baricitinib is an oral medication FDA-approved for rheumatoid arthritis at a 2-mg daily dosage (11) and FDA emergency use authorized for COVID-19 at a 4 mg daily dosage (12-14). The trial will determine whether baricitinib at 2 mg per day 4 mg per day, or both enters the cerebrospinal fluid and attains therapeutic levels, as well as whether it reduces inflammatory biomarkers in the CSF of patients at risk for or with AD and at risk for or with ALS. This basket design is motivated by a common pathogenic mechanism found in these diseases. Following autopsy, brains from both AD and ALS patients exhibit increased innate immune activation

relative to age-matched controls. Moreover, cerebrospinal fluid collected from living patients with diagnoses of subjective cognitive decline, mild cognitive impairment, and ALS revealed elevated levels of interferon signaling, including pPKR, PKR, and pPKR/PKR ratio (1,15). The safety profile of baricitinib is well documented in its package insert.

If this Phase I/II trial demonstrates that baricitinib is safe in AD and ALS patients and achieves therapeutic levels in the CSF as determined by drug concentration and pharmacodynamic biomarkers, then a Phase III clinical trial powered to assess clinical outcomes in AD patients, ALS patients, or both would be warranted.

2.2 Rationale

Converging evidence reveals Type I interferon signaling is robustly active within the central nervous system of subsets of patients with AD and ALS, both in autopsied brains and profiles of CSF of living patients. The Albers lab discovered in animal models that activation of type I interferon signaling leads to propagated neurodegeneration within a neural circuit (8). In cultured human neurons, activation of type I interferon signaling results in neuronal death within 48 hours. Baricitinib, a drug that blocks type I interferon signaling protects cultured human neurons from death evoked by pathogenic cytoplasmic dsRNA. Independently, in computational biology studies of gene expression profiles of AD brains termed DRIAD (drug repurposing in AD), baricitinib was among the leading drugs that reversed the actions of AD (9). We have characterized a signature of type I interferon signaling in the brains and CSF of AD and ALS patients that is specific for this inflammatory mechanism of neuronal death (8).

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Risks associated with Baricitinib

The safety profile of baricitinib is derived from studies of participants with rheumatoid arthritis and described in the baricitinib package insert (OLUMIANT®) (16).

The safety profile of baricitinib in ALS and AD patients is expected to be within the profile reported for patients taking baricitinib for its primary indication of rheumatoid arthritis. The most common adverse reactions (greater than or equal to 1%) were upper respiratory tract infections, nausea, herpes simplex, and herpes zoster.

Less common, but serious adverse events reported in patients receiving baricitinib are outlined below:

Serious Infections

Serious and sometimes fatal infections due to bacterial, invasive fungal, viral, and opportunistic pathogens have been reported in rheumatoid arthritis patients receiving baricitinib. The most

common serious infections included pneumonia, herpes zoster, and urinary tract infections. Among opportunistic infections, tuberculosis, multidermatomal herpes zoster, esophageal candidiasis, pneumocystosis, acute histoplasmosis, cryptococcosis, cytomegalovirus, and BK virus were reported.

Participants in this study may be at an increased risk for COVID-19, although baricitinib has been studied as a drug to reduce the risk of progressing to severe forms of COVID-19 disease. While this is an unknown risk, participants should adhere to CDC guidelines for at-risk populations.

Serious heart-related events(heart attack, stroke)

Based on a completed U.S. FDA review of a large randomized safety clinical trial, it was be concluded there is increased risk of serious heart-related events such as heart attack or stroke with the arthritis and ulcerative colitis medicine, tofacitinib. The FDA has required new and updated warnings for baricitinib in light of these findings. Baricitinib has not been studied in trials similar to the large safety clinical trial with tofacitinib so the risks have not been adequately evaluated. However, since baricitinib shares a mechanism of action with tofacitinib, FDA considers that the medicine will have similar risks.

Death

Based on a completed U.S. FDA review of a large randomized safety clinical trial, it was be concluded there is increased risk of death with tofacitinib. The FDA has required new and updated warnings for baricitinib in light of these findings.

Malignancy and Lymphoproliferative Disorders

Malignancies were observed in clinical studies of baricitinib. Non-melanoma skin cancers have been reported in patients treated with baricitinib. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Thrombosis

Thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis, have occurred. Some of these events have been fatal. Baricitinib should be used with caution in patients who may be at increased risk of thrombosis. Patients with ALS are at increased risk for DVT and PE. If clinical features of DVT/PE or arterial thrombosis occur, patients should be evaluated promptly and treated appropriately.

Gastrointestinal Perforations

Events of gastrointestinal perforation have been reported in clinical studies with baricitinib, although the role of JAK inhibition in these events is not known. Baricitinib should be used with caution in patients who may be at increased risk for gastrointestinal perforation. Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation. Baricitinib can be administered safely through a G-tube. Please refer to the Pharmacy Manual for further details on drug administration.

Laboratory Abnormalities

Neutropenia
Treatment with baricitinib was associated with an increased incidence of neutropenia (absolute neutrophil count (ANC) less than 1000 cells/mm^3) compared to placebo.

Lymphopenia
Treatment with baricitinib was associated with an increased incidence of lymphopenia (absolute lymphocyte count (ALC) less than 500 cells/mm^3). Lymphocyte counts less than the lower limit of normal were associated with infection in patients treated with baricitinib but not placebo.

Anemia
Treatment with baricitinib was associated with an increased incidence of anemia (hemoglobin levels less than 8 g/dL).

Liver Enzyme Elevations
Treatment with baricitinib was associated with increased incidence of liver enzyme elevation. Increases to greater than or equal to 5x and greater than or equal to 10x upper limit of normal (ULN) were observed for both ALT and AST in patients in baricitinib clinical trials. Prompt investigation of the cause of liver enzyme elevation is recommended to identify potential cases of drug-induced liver injury.

Lipid Elevations
Treatment with baricitinib was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Patients should be managed according to clinical guidelines for the management of hyperlipidemia.

Risks associated with Lumbar Puncture
There are potential risks and side effects associated with lumbar punctures (LPs). LP is a standard procedure used in medical practice. The side effects of an LP may include back discomfort, bleeding, headache, pain at the LP site, and infection. Pain during the LP procedure will be prevented or minimized by using local anesthesia. Infection after a LP is very rare, but serious, and will be treated with antibiotics.

About 1 out of 3 people who have a LP develop a post-lumbar puncture headache(17). Post lumbar headaches are more common in females and in people less than 30 years old. This headache can be mild to severe. Atraumatic needs have been shown to reduce the risk of headache and will be used in this study to minimize this risk. There is a 15% headache rate with use of an atraumatic needle(18).

Occasionally the headache can interfere with the study participant's normal daily activities (e.g., work, school). Participants will receive analgesics (pain killers) as needed. If the headache lasts more than 3 days, a blood patch may be performed. This procedure involves taking blood from the

participant and injecting it in the same place where the spinal needle was put in during the LP. The clotting of the blood in this space should stop further fluid leaking and stop the headache.

Risks associated with Fluoroscopic Lumbar Puncture:
A fluoroscopic LP will be performed if standard LP cannot be done. The main risk in this procedure is exposure to radiation. The total amount of radiation exposure to participants taking part in this study is equal to a whole-body exposure of up to 0.65 milliSieverts (mSv) per fluoroscopic LP. A possible effect that could occur at doses used in this study is a slight increase in the risk of developing cancer later in life. Since the side effects of radiation can be cumulative, the study staff and investigators will collect information on prior radiation exposure to determine whether it is safe to receive a dose of radiation for the purposes of this research study.

Risks associated with Recombination Zoster Vaccination
A sore arm with mild or moderate pain is very common after recombinant shingles vaccine, affecting about 80% of vaccinated people. Redness and swelling can also happen at the site of the injection. Tiredness, muscle pain, headache, shivering, fever, stomach pain, and nausea happen after vaccination in more than half of people who receive recombinant shingles vaccine. In clinical trials, about 1 out of 6 people who got recombinant zoster vaccine experienced side effects that prevented them from doing regular activities. Symptoms usually went away on their own in 2 to 3 days.

2.3.2 Known Potential Benefits

There are no known benefits for participating in this trial. Patients who participate will add to the collective knowledge of the actions of baricitinib in patients with AD and ALS.

3 OBJECTIVES

3.1 Study Objectives

3.1.1 Primary Objective

The primary objectives of the study are:

- To assess whether 8 weeks of an oral dosage of baricitinib 2 mg per day, 4 mg per day, or both achieves measurable levels of baricitinib in the CSF of patients with AD, ALS, and asymptomatic carriers of an ALS-causative gene.
- To determine whether 8 weeks of an oral dosage of baricitinib 2 mg per day, 4 mg per day, or both decreases levels of the inflammatory biomarker chemokine ligand 2 (CCL2) in the CSF of patients with AD, ALS, and asymptomatic carriers of an ALS-causative gene.

3.1.2 Secondary Objectives

The secondary objectives of the study are:

- To determine whether an oral dosage of baricitinib 2 mg per day, 4 mg per day, or both decreases levels of the inflammatory biomarkers interleukin-6 (IL-6), phospho-protein kinase R (pPKR), PKR, pPKR / PKR ratio, C-X-C motif chemokine ligand 10 (CXCL10), or interferon Gamma (IFNG) in the CSF of patients with AD, ALS, and asymptomatic carriers of an ALS-causative gene.
- To determine whether 8 weeks of an oral dosage of baricitinib 2 mg per day, 4 mg per day, or both decreases levels of neuronal death biomarkers of neurofilament light chain (NfL), tau, or phospho-tau in CSF or TAR DNA-binding protein 43(TDP-43) levels in the plasma in patients with AD, ALS, and asymptomatic carriers of an ALS-causative gene.
- To determine whether the measured concentration of baricitinib in the CSF or blood (pharmacokinetics) after 8 weeks of an oral dosage of baricitinib 2 mg per day, 4 mg per day, or both correlates with the changes in CSF biomarkers (pharmacodynamics).
- To determine whether 8 weeks of an oral dosage of baricitinib 2 mg per day, 4 mg per day, or both is safe and tolerable in patients with AD, ALS, and asymptomatic carriers of an ALS-causative gene.

3.1.3 Exploratory Objectives

The exploratory objectives of the study are:

- To determine whether 8 weeks of an oral dosage of baricitinib 2 mg per day, 8 weeks or 16 weeks of baricitinib 4 mg per day, or both decreases levels of the inflammatory

biomarkers CCL2, IL-6, pPKR, PKR, pPKR / PKR ratio, CXCL10, or IFNG in the plasma of patients with AD, ALS, and asymptomatic carriers of an ALS-causative gene.
- To determine whether changes in clinical outcomes correlate with CSF drug concentration or with changes in CSF biomarkers after 8 weeks of an oral dosage of baricitinib 2 mg per day, 4 mg per day, or both.
- To collect CSF for further biomarker discovery efforts via proteomics, dsRNA-seq, and other unbiased chemical profiling methods.
- To refine the CSF inflammatory signature for AD and ALS patients and identify factors that predict diminishment of the CSF inflammatory signature after 8 weeks of an oral dosage of baricitinib 2 mg per day, 4 mg per day, or both.

3.2 Study Outcome Measures

3.2.1 Primary Outcome Measures

The primary outcome measures for the study are:
- Level of free baricitinib in the CSF.
- Change in the level of the inflammatory biomarker CCL2 in the CSF (from baseline to 8-weeks and to 16-weeks).

3.2.2 Secondary Outcome Measures

The secondary outcome measures for the study are:
- Changes in the inflammatory biomarkers pPKR, PKR, pPKR/PKR ratio, CXCL10, and IFNG in the CSF (from baseline to 8-weeks and to 16-weeks).
- Changes in the neuronal death biomarkers NfL, tau, and phospho-tau in the CSF and TDP-43 in plasma (from baseline to 8-weeks and to 16-weeks).
- Association between drug concentration(pharmacokinetics) and CSF biomarkers (pharmacodynamics).
- Treatment-emergent adverse events.
- Permanent discontinuation of study drug due to study drug-related AEs.

3.2.3 Exploratory Outcome Measures

The exploratory outcome measures for the study include:
- Changes in the inflammatory biomarkers IL-6, CCL2, pPKR, PKR, pPKR/PKR ratio, CXCL10, and IFNG in the plasma (from baseline to 8-weeks, to 16-weeks and to 24-weeks).
- Changes in clinical outcomes (from baseline to 24-weeks) relative to previous trajectories, when available.
- Change in Accessible Remote Olfactory Mediated Health Assessments (AROMHA) olfactory battery score.

4 STUDY DESIGN

4.1 Overall Study Design and Plan

During the enrollment period, approximately 40 participants will be enrolled from up to 2 centers in the United States. Each site will enroll in parallel. It is expected that each site will enroll both AD and ALS patients; however, asymptomatic carriers of an ALS-causative gene will only be enrolled at the MGH site. Consenting individuals will be screened for eligibility, including collection of CSF by LP and testing of CCL2 levels. Up to 20 eligible participants (10 AD and 10 ALS or asymptomatic carriers of an ALS-causative gene, with a limit of 5 asymptomatic carriers) will be enrolled and receive treatment with baricitinib 2 mg per day for 8 weeks, followed by baricitinib 4 mg per day for 16 weeks. Visits for enrolled participants will occur at Baseline, Week 1, Week 8, Week 9, Week 16, and Week 24 or a Final Safety Visit. There will be a Follow-up Telephone Call 28 to 33 days after last dose of study drug. In addition to the LP at screening, enrolled participants will undergo LPs at Baseline, Week 8, and Week 16.

All visit windows are consecutive calendar days and are calculated from Day 0, the day of the Baseline Visit.

4.2 Interim Analyses

Interim analyses will be conducted by the chief biostatistician to assess the ability of baricitinib to cross the blood-brain barrier and enter the CSF or to exert a pharmacodynamic effect on CCL2 in the CSF. One of the following two PK and PD criteria must be met in at least one participant to continue enrollment beyond 10 participants:

1. PK criterion: free baricitinib concentration in the CSF > 0.1 μM from samples collected at the Week 8 or Week 16 LP, or
2. PD criterion: 25% reduction of CCL2 concentration in the CSF from baseline to the Week 8 or Week 16 LP.

Interim analyses will be conducted approximately monthly (as long as there are new results to review) after the first participant completes Week 8 until at least 1 participant meets the continuation criterion or until 10 participants have completed the Week 8 LP and none has met the continuation criterion. Enrollment will be suspended after 10 participants enroll if no participant has yet met the continuation criterion, including no fewer than 2 AD, MCI, or SCD participants and no fewer than 2 ALS participants (of whom no more than 1 may be an asymptomatic carrier of an ALS-causative gene). No additional interim analyses will be conducted after the first participant meets the continuation criterion. Enrollment will be terminated if the continuation criterion has not been observed after 10 participants complete follow-up.

4.3 Study Centers

This study will be conducted at up to 2 centers in the US.

4.4 Study Duration

Participants will remain on treatment until the Week 24 Visit. Participants who withdraw consent or early terminate from the study will be asked to complete a Final Safety Visit when they notify the site of their desire to end participation or as soon as possible thereafter. All participants will be asked to complete a Follow-up Telephone Call 28 to 33 days after their last dose of study drug.

4.5 Protocol Adherence

Each Site Investigator (SI) must adhere to the protocol detailed in this document except as required to protect the life or physical well-being of a participant in an emergency and must agree that any changes to the protocol must be approved by the NCRI Coordination Center (CC) and single Institutional Review Board(sIRB). Each SI will be responsible for enrolling only those study participants who have met protocol eligibility criteria.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Number of Study Participants

Up to 20 participants (10 AD and 10 ALS) will be enrolled and receive treatment.

The 10 AD participants will include patients with Subjective Cognitive Decline (SCD), Mild neurocognitive disorder (mild cognitive impairment), or major neurocognitive disorder (possible or probable AD).

The 10 ALS participants may include up to 5 asymptomatic carriers of an ALS-causative gene. The asymptomatic carriers of an ALS-causative gene will only be enrolled at the MGH site.

5.2 Inclusion and Exclusion Criteria

5.2.1 Inclusion Criteria

Study participants meeting all of the following criteria will be allowed to enroll in the study:

1. Must be 55-90 years old, inclusive and have one of the following:
   - Subjective cognitive decline(SCD)
   - Minor neurocognitive disorder(mild cognitive impairment(MCI))
   - Major neurocognitive disorder(possible or probable AD)

OR

Must be 18-80 years old, inclusive and have one of the following:
   - Sporadic or familial ALS diagnosed as possible, laboratory-supported probable, probable, or definite as defined by the revised El Escorial criteria
   - Asymptomatic carrier of an ALS-causative mutation per CLIA-certified genetic testing results (MGH site only)
2. Screening CSF level of
   - CCL2 level ≥ 250 pg/mL
3. Must have received the Recombinant Zoster Vaccine (RZV, also known as Shingrix) within 4 years prior to treatment initiation. Note: Only one dose of RZV is needed prior to the Baseline Visit.
   - Investigators should review the vaccination status of their patients and follow the local guidelines for non-live vaccination of patients.
4. For participants with ALS:
   - Must either not be taking or be taking any FDA approved treatment for ALS for at least 30 days or at least 1 cycle prior to screening.
   - ALSFRS-R score ≥ 27

- Must be ambulatory, defined as able to walk at least within the home every day. Use of gait assistive devices is allowed. Some use of a wheelchair is also allowed.
- Greater than 12-month life expectancy in the opinion of the investigator.

For participants with AD:

- MoCA score ≥ 8
- For participants with major neurocognitive disorder(possible or probable AD), the participant must have one study partner that can accompany them to every visit and co-sign any informed consent document.
- For participants with mild neurocognitive disorder or subjective cognitive decline, participants must have one study partner available to participate in the Baseline and Week 24 Visits.
- Must either not be taking or be on a stable dose of any FDA approved treatment for AD for at least 30 days prior to screening, with the exception of the prohibited medications (listed in section 6.7.1).

5. Ability to medically undergo LP in the opinion of the investigator (e.g., no bleeding disorder, allergy to local anesthetics, prior lumbar surgery which might make LP difficult, a skin infection at or near the LP site, evidence of high intracranial pressure, or anticipated difficulty getting into position for LP).
6. Capable of providing informed consent and following study procedures.

- In the case that a participant lacks the ability to provide informed consent, informed consent will be obtained from the participant's surrogate representative and assent obtained from the participant.

5.2.2 Exclusion Criteria

Study participants meeting any of the following criteria during screening evaluations will be excluded from entry into the study:

1. Women who are pregnant, breastfeeding, or planning to become pregnant during the trial.
2. Any unstable clinically significant medical condition other than ALS or AD (e.g., within six months of baseline, including but not limited to myocardial infarction, angina pectoris, congestive heart failure, or neoplasm undergoing active treatment).
3. Active cancer or history of cancer, except for the following: basal cell carcinoma, cervical carcinoma in situ, prostatic carcinoma in situ, or other malignancies curatively treated and with no evidence of disease recurrence for at least 5 years. Active cancer includes cancers with current disease manifestations or therapy that could adversely affect participant safety and longevity, create the potential for drug-drug interactions, or compromise the interpretation of study results.
4. History of diverticulitis or bowel perforation.
5. Active ulcerative colitis, Crohn's disease, and history of peptic ulcer disease within the past 5 years or after the age of 65.
6. Active, serious infection, including localized infection in the opinion of the investigator.

7. Positive for latent or active tuberculosis (TB). Note: Patients with a history of latent or active TB must have had an adequate course of treatment documented prior to study participation.
8. Evidence of active hepatitis B or C infection.
9. History of severe hepatic or renal impairment.
10. eGFR < 60 mL/min/1.73 m^2
11. Have any of the following specific abnormalities on screening laboratory tests:

- ALT or AST >2.5x upper limits of normal (ULN)
- Alkaline phosphatase (ALP) ≥2x ULN
- Total bilirubin ≥1.5x ULN, **Note:** patients with elevated bilirubin secondary to Gilbert's disease are eligible to participate in the study.
- Hemoglobin <10 g/dL (100.0 g/L)
- Total white blood cell count <3000 cells/μL (<3.00 x 10^3/μL or <3.00 billion/L)
- Neutropenia (absolute neutrophil count [ANC] <1500 cells/μL) (<1.50 x 10^3/μL or <1.50 billion/L)
- Lymphopenia (lymphocyte count <1000 cells/μL) (<1.00 x 10^3/μL or <1.00 billion/L)
- Thrombocytopenia (platelets <100,000 cells/μL) (<100 x 10^3/μL or <100 billion/L)
- Laboratory abnormalities in vitamin B12, thyroid stimulating hormone (TSH), or other common laboratory parameters that might contribute to cognitive dysfunction

12. Personal history of pulmonary embolus (provoked or unprovoked) or deep vein thrombosis, or a history of unprovoked pulmonary embolus in a first-degree family member.
13. Treatment with anticoagulants that, in the opinion of the investigator, would compromise the safety of the participant.
14. Previous therapy with baricitinib.
15. Current use of strong Organic Anion Transporter 3(OAT3) inhibitors (e.g., probenecid) or other prohibited medication (refer to Section 6.7.1) within 5.5 half-lives or 30 days of screening, whichever is longer.
16. Receiving other experimental interventions for AD or ALS (with the exception of FDA approved drugs used for their indication and over the counter supplements administered outside of therapeutic trials) within 5.5 half-lives or 30 days of screening, whichever is longer.
17. Received live vaccine within 12-weeks of screening or are expected to receive a live vaccine during the course of the study.
18. Use of permanent assisted ventilation (invasive ventilation via tracheostomy, or >22 hours of non-invasive ventilation per day, e.g., via BiPAP).
19. Have had any major surgery within 8 weeks prior to screening or will require major surgery during the study that, in the opinion of the investigator, would pose an unacceptable risk to the patient. **Note:** Placement of a gastrostomy tube and an intravenous port are not considered major surgery.

5.3 Treatment Assignment Procedures

Each participant who meets all eligibility criteria and completes a Baseline Visit will be treated with baricitinib 2 mg per day for 8 weeks, followed by baricitinib 4 mg per day for 16 weeks.

5.4 Permanent Discontinuation of Study Drug

A participant may choose to discontinue use of study drug at any time. A study participant's use of study drug will be permanently discontinued by the SI or designee if:

- Any clinical adverse event (AE), laboratory abnormality, concurrent illness, or other medical condition or situation occurs such that continued exposure to study drug would not be in the best interest of the participant.
- The participant begins use of a prohibited medication.
- The participant is non-compliant or lost to follow up.

If the SI or designee is concerned about the use of a prohibited medication or other safety issues, then the study drug may have to be interrupted or discontinued. Any participant who is on study drug and needs to begin the use of any prohibited medication must immediately discontinue use of study drug and should not begin use of the prohibited medication before an appropriate wash-out period of 30 days occurs. A Follow-up Telephone Call should be conducted 28 to 33 days after their last dose of study drug. The Follow-up Telephone Call may be superseded by a normally scheduled study visit if timing is appropriate. Loss to follow-up should be prevented whenever possible.

If two or more similar serious adverse events result in permanent discontinuation of study drug and are deemed to be at least possibly related to study drug, the DSMB will review these events promptly and make recommendations about potential changes to the study, including possible changes to protocol, updates to the informed consent form, or terminating the study early.

5.5 Early Termination and Withdrawal of Consent

A participant may choose to terminate from the study or withdraw consent at any time.

Early termination occurs when a participant indicates that they no longer wish to participate in future study procedures after completing the screening period. The participant should be encouraged to complete a Final Safety Visit when they notify the site of their desire to end participation or as soon as possible thereafter. If the participant is permanently discontinuting study drug at the same time, then the procedures for permanent discontinuation of study drug (Section 5.4) should be followed. Participants who early terminate may still be contacted by study staff.

Participants who withdraw consent are no longer research participants and should not be contacted by study staff to discuss their participation or collect further data. Site investigators should ensure that the distinction between early termination and withdrawal of consent is clear to participants when they choose to end their participation. Participants who withdraw consent should follow the procedures outlined above for early terminated participants. If the participant also wishes to exclude their previously collected personal health information, he or she should notify the site

through an authorized letter and his or her biosamples will be destroyed and his or her data will no longer be included as part of the results for this study.

Site study staff may lose contact with a participant for many reasons. Please refer to the Site MOP for guidance on the procedure if a participant is suspected to be lost to follow up.

5.6 Suspension or Termination of Study

This study may be suspended or prematurely terminated if, in the opinion of the investigator, there is sufficient reasonable cause. Written notification, documenting the reason for study termination, will be provided to the investigator or sponsor by the suspending or terminating party.

Circumstances that may warrant suspension or termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Enrollment is unsatisfactory.
- Insufficient adherence to protocol requirements.
- Data that are not sufficiently complete and evaluable.
- Plans to modify, suspend or discontinue the development of the study drug.

If the study is suspended or prematurely terminated, the sponsor will promptly inform the investigators/institutions, and the regulatory authority(ies) of the suspension or termination and the reason(s) for the suspension or termination. The sIRB will also be informed promptly and provided the reason(s) for the suspension or termination by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

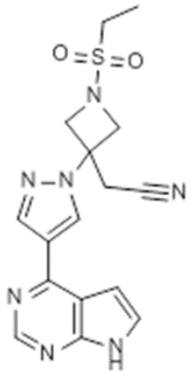
6 TREATMENTS ADMINISTERED

6.1 Treatments

6.1.1 Study Product Description

Baricitinib (Olumiant®, Eli Lilly and Company) is a JAKinhibitor with the chemical name 1-(ethylsulfonyl)-3-[4-(7H- pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl acetonitrile. Baricitinib has an empirical formula of $C_{16}H_{17}N_7O_2S$ and a molecular weight of 371.42 g/mol.

Baricitinib has the following structural formula:



Baricitinib tablets contain a recessed area on each face of the tablet surface and are available for oral administration as debossed, film-coated, immediate-release tablets. The 2 mg tablet is light pink, oblong, debossed with “Lilly” on one side and “2” on the other.

Each tablet contains 2 mg of baricitinib and the following inactive ingredients: croscarmellose sodium, magnesium stearate, mannitol, microcrystalline cellulose, ferric oxide, lecithin (soya), polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

6.2 Acquisition

Each site will obtain baricitinib from their institution’s local pharmacy or from supply donated from Eli Lilly, dependent upon availability.

6.3 Formulation, Packaging, and Labeling

Study participants will take one 2 mg tablet of baricitinib by mouth once per day for the first 8 weeks. Participants will take two 2 mg tablets of bariticitinib by mouth once per day for the remaining 16 weeks.

Baricitinib is prepackaged in bottles containing 30 tablets and ready for oral administration. Study drug will be dispensed at the following visits: Baseline, Week 8, and Week 16. Please refer to the Pharmacy Manual for further details on drug dispensing at specified visits.

6.3.1 Product Storage and Stability

Study drug should be stored at 20° to 25°C (68° to 77°F); excursions are permitted to 15° to 30°C (59° to 86°F).

6.3.2 Dosage, Preparation and Administration of Study Intervention/Investigational Product

Since baricitinib is FDA-approved for rheumatoid arthritis, alopecia, and COVID-19, we will follow the guidelines in the package insert. Baricitinib is given orally with or without food. If needed, baricitinib tablet can administered through a G-tube. Please refer to the Pharmacy Manual for further details on drug administration.

Baricitinib should be taken at roughly the same time every day, except for days when an LP will be performed. At study visits with LPs, participants will dose in clinic from home supply and time of dose will be recorded by the study team.

6.4 Modification of Study Intervention/Investigational Product for a Participant

Any dosage adjustment, including the reason for and dates of adjustment, will be documented in the CRF for each participant requiring this manipulation. The SI or licensed physician Sub-Investigator may interrupt, reduce, or discontinue the study drug in its entirety for adverse events (AEs) thought to be related to study drug or for other reason during the trial (the reason for and dates of suspension must be documented).

If the event is serious or life threatening and deemed to be definitely drug related, study drug should be discontinued immediately. Study participants must remain off study drug permanently. Participants may not resume study drug. All AEs will be followed to resolution or 28 to 33 days after last dose of study drug.

6.4.1 Serious Infections and Cytopenias

Baricitinib should not be administered in patients with active infection. If a participant develops a serious infection, administration of baricitinib should be interrupted until the infection is controlled. Dose can be resumed or reduced at the investigator’s discretion once the infection is controlled.

Dosage of baricitinib should be modified in cases of lymphopenia, neutropenia, anemia, and thrombocytopenia according to the tables below:

Low Absolute Lymphocyte Count (ALC)	
Lab Value (cells/mm^3)	**Recommendation**
ALC greater than or equal to 500	Maintain dose
ALC less than 500	On 4 mg dose, interrupt baricitinib until ALC greater than or equal to 500, resume at 2 mg dose On 2 mg dose, do not resume dosing with baricitinib

Low Absolute Neutrophil Count (ANC)	
Lab Value (cells/mm^3)	**Recommendation**
ANC greater than or equal to 1000	Maintain dose
ANC less than 1000	On 4 mg dose, interrupt baricitinib until ANC greater than or equal to 1000, resume at 2 mg dose On 2 mg dose, do not resume dosing with baricitinib

Low Hemoglobin Value	
Lab Value (g/dL)	**Recommendation**
Greater than or equal to 8	Maintain dose
Less than 8	On 4 mg dose, interrupt baricitinib until hemoglobin greater than or equal to 8, resume at 2 mg dose On 2 mg dose, do not resume dosing with baricitinib

Platelets	
Lab Value (plts/uL)	**Recommendation**
Greater than or equal to 50K	Maintain dose
Less than 50K	On 4 mg dose, interrupt baricitinib until platelets greater than or equal to 50, resume at 2 mg dose On 2 mg dose, do not resume dosing with bariticinib

Elevated ALT and/or AST	
Lab Value	**Recommendation**
Less than 5x ULN	Maintain dose
Greater than or equal to 5x ULN	Interupt baricitinib until ALT and/or AST less than 5x ULN *Please refer to Dosage Discontinuation(Section 6.4.2) for study drug discontinuation thresholds related to elevated liver function tests.

If lab abnormalities occur, clinical monitoring may be required. Please refer to the Study MOP for additional guidance.

Bariticinib can be re-escalated per investigator discretion after discussion with the Medical Monitor.

6.4.2 Dosage Discontinuation

Reasons for discontinuation of study medication may include an AE, Medical Monitor or Site Investigator recommendation, study termination, protocol deviation, loss to follow-up, participant request, or death. All serious adverse events (SAEs) that occur in a participant who has discontinued early must be recorded and reported within 24-hours of awareness.

Discontinuation of the investigational product for abnormal liver tests should be considered by the investigator when a participant meets any of the following conditions:

- ALT or AST >8x ULN
- ALT or AST >5x ULN for more than 2 weeks after temporary interruption of investigational product
- ALT or AST >3x ULN and total bilirubin level (TBL) >2x ULN or international normalized ratio (INR) >1.5 (**Note:** patients with elevated bilirubin secondary to Gilbert's disease do not need to discontinue study drug)
- ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP >3x ULN that is deemed to be of liver origin and drug-related
- ALP >2.5x ULN and TBL >2x ULN(**Note:** patients will elevated bilirubin secondary to Gilberts disease do not need to discontinue study drug.)
- ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, or eosinophilia(>5%)

In addition, participants will be discontinued from investigational product in the following circumstances:

- Malignancy (except for basal cell carcinoma, cervical carcinoma in situ, and prostatic carcinoma in situ)
- HBV DNA detected with a value above limit of quantitation
- Development of a venous thromboembolism(VTE) during the study

Participants who discontinue study drug prematurely (whether or not they are continuing on the study or early terminating) will be encouraged to participate in a Follow-up Telephone Call 28 to 33 days after their last dose of study drug.

SAEs will be followed for resolution for 28 to 33 days after a participant's last dose of study drug, regardless of whether they prematurely discontinued study drug or completed 24 weeks of treatment.

6.5 Study Drug Accountability Procedures

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6.6 Assessment of Participant Compliance with Study Drug

Participants will be instructed to return empty and unused study medication containers throughout the study and at the Final Safety Visit. Site personnel will review returned and unused study medication to determine compliance during each clinic visit.

6.7 Prior and Concomitant Therapy

Throughout the study, SIs may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care provided that the medications are licensed in the US. Study participants should not receive other experimental agents during the study. This includes marketed agents at experimental dosages that are being tested for the treatment of ALS or AD. Any investigational therapy being used or evaluated for the treatment of ALS or AD is prohibited 30 days or 5.5 half-lives prior to the Screening Visit, whichever is longer and throughout the study. For investigator support, a list of experimental therapies will be maintained.

All concomitant medications and treatments and significant non-drug therapies including supplements and assistive devices received by a participant should be recorded on the appropriate source document and eCRF. COVID-19 vaccinations and booster shots will also be documented as concomitant medications.

6.7.1 Prohibited Medications and Contraindications

<u>Prohibited Medications</u>
Participants must stop taking prohibited medications 30 days or 5.5. half-lives prior to the Screening Visit, whichever is longer.

Throughout the course of the trial, study participants should not take the following medications. If an investigator learns that a participant has begun therapy with any of these medications, this should be reported to the Medical Monitor and Coordination Center immediately and action should

be taken to discontinue the prohibited medication. If, for safety or health reasons, or by participant choice, the prohibited medication cannot be stopped, then the study medication should be stopped.

Prohibited medications include:

- Experimental interventions for AD or ALS (with the exception of FDA approved drugs used for their indication and over the counter supplements administered outside of therapeutic trials)
- Amyloid Beta-Directed Antibodies:
    - Aducanumab (Aduhelm)
    - Lecanemab (Leqembi)
    - Donanemab
- Strong OAT3 Inhibitors:
    - Probenecid
- Biologic DMARDs:
    - Jakafi (ruxolitinib)
    - Xeljanz (tofacitinib)
    - Humira (adalimumab)
    - Enbrel (etanercept)
    - Arava (leflunomide)
    - Otrexup, Rasuvo, Rheumatrex and Trexall (methotrexate)
    - Azulfidine (Sulfasalazine)
    - Rituxan (rituximab)
    - Remicade (infliximab)
    - Cimizia (certolizumab pegol)
    - Simponi (golimumab)
    - Kineret (anakinra)
    - Actemra (tocilizumab)
- Potent immunosuppresants:
    - Azasan (azathioprine)
    - Neoral, Sandimmune, and Gengraf (cyclosporine)
    - Prograf (tacrolimus) (note: topical cream used to treat eczema not excluded)
- Live-attenuated or viral vector vaccines:
    - Measles
    - Mumps
    - Rubella
    - Vaccinia
    - Rotavirus
    - Varicella
    - Zostavax Zoster
    - Intranasal influenza
    - COVID-19 (Please note, all COVID vaccines are viral vector. J&J / Janssen is a AAV viral vector.)

Pregnancy & Nursing Mothers

There are no adequate and well-controlled studies in pregnant women. Participants or partners of male participants should not become pregnant during the study or for at least 1 week after stopping study drug. If a female participant becomes pregnant, study treatment must be discontinued immediately. If a female participant becomes pregnant during the course of the study, the Medical Monitor and Coordination Center should be contacted immediately.

It is not known if baricitinib is excreted in breast milk. Caution should be exercised; women should not breastfeed during treatment with baricitinib.

7 STUDY SCHEDULE

No study procedures should be performed prior to the signing of the informed consent form (ICF). All participants will sign an ICF prior to undergoing any study tests or procedures.

For ALS participants taking IV or oral edaravone, all LP visits(Screening, Baseline, Week 8, and Week 16) must occur at least 7 days after the last dose of edaravone in a given cycle and can occur up until the participant begins dosing for the subsequent edaravone cycle.

At Week 8,Week 16, and Week 24, it is recommended that administration of study drug is one of the first procedures completed. Participants will dose in clinic from home supply and the time of dosing will be recorded by the study team. The research blood draw must be done before the LP and 1 hour (± 10 minutes) after dosing. The LP must be performed within 2 to 4 hours after dosing, ideally 2 hours post-dose. Apart from the blood draws and LP, the order of testing can be performed at the discretion of each Site Investigator (SI).

Option for Remote Visits
Study visits will be conducted in clinic unless otherwise specified. Participants have the option for Week 1 and Week 9 Visits to be conducted in clinic or remotely. Remote visits will include local safety lab collection as well as a telehealth or telephone visit (i.e., institutional-approved, HIPAA-compliant remote method). The following assessments will be collected via telehealth or telephone visit: C-SSRS, survival assessment, concomitant medication review, and AE review. Vital signs will not be collected at remote visits. If safety labs will be collected at a local facility outside of the study center, please refer to the Site MOP for guidance on collecting the appropriate documentation from the facility and notify the NCRI Project Management team before use.

Visit windows are consecutive calendar days and the target visit dates are calculated from the Baseline Visit.

Participants who withdraw consent or early terminate from the study will be asked to complete a Final Safety Visit when they notify the site of their desire to end participation or as soon as possible thereafter. All participants will be asked to have a Follow-up Telephone Call 28 to 33 days after their last dose of study drug.

7.1 Screening Visit

Screening visit activities can be completed over a period of 30 days except for the first dose of the Shingrix vaccine, if not already received within 4 years prior to treatment initiation. The following procedures will be performed in clinic to determine the participant's eligibility for the study:

- Obtain written informed consent from participant (if feasible) and caregiver (if applicable)
- Assess inclusion and exclusion criteria
- Obtain medical history and demographics
- Obtain ALS or AD diagnosis history
- Assess El Escorial Criteria (ALS patients only)

- Measure vital signs including height and weight
- Perform physical examination
- Perform neurological examination
- Perform 12-lead electrocardiogram (ECG)
- Administer ALSFRS-R questionnaire (ALS patients only)
- Perform Slow Vital Capacity (SVC) (ALS patients only)
- Administer Montreal Cognitive Assessment (MoCA) (AD only)
- Administer the Baseline Columbia-Suicide Severity Scale (C-SSRS) questionnaire
- Collect blood sample for:
    - Clinical laboratory assessments, including Hematology (CBC with differential), Comprehensive Metabolic Panel with Liver Function Tests and Coagulation
    - Vitamin B12, Thyroid Stimulating Hormone(TSH) and Folate
    - HIV, Hepatitis B and Hepatitis C
    - Research (Biomarker analysis, immune cell profiling and storage)
- Collect urine sample for:
    - Urinalysis
    - Urine Pregnancy Test (for woman of childbearing potential [WOCBP]) with result prior to LP
- Perform testing for Tuberculosis (TB)
- Perform LP for CSF collection
    - Note: Review of recent CBC and Coagulation results is required to determine if LP can be performed.
    - Note: Results of CSF examination are required to determine study eligibility. If a patient had a LP and CSF collected within 6 months of the Screening Visit, please contact the NCRI Coordination Center to confirm if this CSF sample could be used in place of the screening LP. Allowing CSF from prior LP will be determined on a case by case basis.
- Administer 1st dose of Recombinant Zoster Vaccine (RZV; also known as Shingrix) unless participant has documentation of vaccination within 4 years prior to treatment initiation
    - Note: The first dose of RZV should be administered after all other eligibility criteria have been confirmed and at least 14 days prior to the Baseline Visit.
- Review and document concomitant medications and therapies
- Assess and document Adverse Events (AEs) after participant signs ICF

7.1.1 Screen Failures

Any participant who signs consent will be considered enrolled in the study. The Screening period starts when a participant signs consent and ends with drug initiation at the Baseline Visit. Any enrolled participant who fails to complete the screening period will be considered a screen fail. If a participant fails screening, *at a minimum*, the following information should be captured and entered in the Electronic Data Capture (EDC) System:

- Inclusion/Exclusion criteria
- Demographics
- Reason for screen failure

7.2 Baseline Visit

This visit will take place 53 to 56 days after the Screening LP is performed. **The participant should take their first dose of study drug after all other visit activities have been completed**. The following procedures will be performed:

- Confirm eligibility criteria are still met
- Measure vital signs & weight
- Administer ALSFRS-R questionnaire (ALS patients only)
- Optional: Perform SVC (ALS patients only)
- NIH Toolbox (Asymptomatic carriers of an ALS-causative gene only, MGH site only)
- Administer Neuropsychiatric Inventory Questionnaire (NPI-Q) (AD patients only)
- Administer Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) (AD patients only)
- Administer AROMHA olfactory battery
- Administer the Since Last Visit C-SSRS questionnaire
- Perform survival assessment
- Collect blood sample for:
    - Clinical laboratory assessments, including Hematology (CBC with differential), Comprehensive Metabolic Panel with Liver Function Tests, Coagulation and a Lipid panel.
    - Research (for pre-dose PK, Biomarker analysis, Immune cell profiling & storage)
    - Genetic Testing
- Collect urine sample for:
    - Urinalysis
    - Urine Pregnancy Test (for WOCBP)
    - Future Research
- Perform LP for CSF collection
    - Note: Review of recent CBC and Coagulation results are required to confirm if LP can be performed.
- Review and document concomitant medications and therapies
- Assess and document AEs
- Dispense study drug
- Administer first dose of study drug and record time of administration
    - Start barticinib 2mg once per day dosing
    - Participant should be observed at the site for 60 minutes by an appropriate healthcare staff member according to the site's institutional/state regulations to assess medical status and any immediate reaction to study drug

7.3 Week 1 Visit

This visit will take place 7 ±2 days after the Baseline Visit. This visit can be conducted in clinic or remotely. The following procedures will be performed:

- Measure vital signs & weight (In clinic visits only)
- Administer the Since Last Visit C-SSRS questionnaire
- Perform survival assessment

- Collect blood sample for:
    - Clinical laboratory assessments, including Hematology (CBC with differential), Comprehensive Metabolic Panel with Liver Function Tests and Coagulation
- Collect urine sample for:
    - Urinalysis
    - Urine Pregnancy Test (for WOCBP)
- Review and document concomitant medications and therapies
- Assess and document AEs

7.4 Week 8 Visit

This visit will take place 56 (- 4 days or +1 day) after the Baseline Visit. **The participant should take study drug from home supply at the site upon beginning this visit due to timing of LP and research blood draw.** The following procedures will be performed:

- Administer study drug in clinic from home supply and record time of administration
- Administer 2nd dose of RZV at this visit (or at any visit 2 to 6 months after 1st dose per CDC guidance) unless participant has documentation of RZV within 4 years prior to treatment initiation.
- Measure vital signs & weight
- Administer ALSFRS-R questionnaire (ALS patients only)
- Optional: Perform SVC (ALS patients only)
- Administer the Since Last Visit C-SSRS questionnaire
- Perform survival assessment
- Collect blood and urine sample for:
    - Clinical laboratory assessments, including Hematology (CBC with differential), Comprehensive Metabolic Panel with Liver Function Tests, Coagulation and a Lipid Panel.
    - Research (for PK, Biomarker analysis, Immune cell profiling and storage)
- Collect urine sample for:
    - Urinalysis
    - Urine Pregnancy Test (for WOCBP) with result prior to LP
    - Future Research
- Perform LP for CSF collection
    - Note: Review of recent CBC and Coagulation results are required to confirm if LP can be performed.
- Review and document concomitant medications and therapies
- Assess and document AEs
- Perform study drug accountability and collect all unused drug and empty containers
- Dispense study drug
    - Start baricitinib 4 mg once per day dosing

7.5 Week 9 Visit

This visit will take place 63 +2 days after the Baseline Visit. This visit can be conducted in clinic or remotely. The following procedures will be performed:

- Measure vital signs & weight (In clinic visits only)
- Administer the Since Last Visit C-SSRS questionnaire
- Perform survival assessment
- Collect blood sample for:
    - Clinical laboratory assessments, including Hematology (CBC with differential), Comprehensive Metabolic Panel with Liver Function Tests and Coagulation
- Collect urine sample for:
    - Urinalysis
    - Urine Pregnancy Test (for WOCBP)
- Review and document concomitant medications and therapies
- Assess and document AEs

7.6 Week 16 Visit

The Week 16 Visit will take place 112 ± 4 days after the Baseline Visit. **The participant should take study drug from home supply at the site upon beginning this visit due to timing of LP and blood draw.**

- Administer study drug in clinic from home supply and record time of administration
- Measure vital signs & weight
- Administer the Since Last Visit C-SSRS questionnaire
- Perform survival assessment
- Collect blood sample for:
    - Clinical laboratory assessments, including Hematology (CBC with differential), Comprehensive Metabolic Panel with Liver Function Tests, Coagulation and a Lipid Panel.
    - Research (for PK, Biomarker analysis, Immune cell profiling and storage).
- Collect urine sample for:
    - Urinalysis
    - Urine Pregnancy Test (for WOCBP) with result prior to LP
    - Future Research
- Perform LP for CSF collection
    - Note: Review of recent CBC and Coagulation results are required to confirm if LP can be performed.
- Review and document concomitant medications and therapies
- Assess and document AEs
- Perform study drug accountability and collect all unused drug and empty containers
- Dispense study drug
    - Continue baricitinib 4mg once per day dosing.

7.7 Week 24 Visit/Final Safety Visit

The Week 24 Visit will take place 168 ± 4 days after the Baseline Visit. The following procedures will be performed at this visit:

- Administer study drug in clinic from home supply and record time of administration
- Measure vital signs & weight
- Perform physical examination
- Perform neurological examination
- Administer ALSFRS-R questionnaire (ALS patients only)
- Perform SVC (ALS patients only)
- NIH Toolbox (Asymptomatic carriers of an ALS-causative gene only, MGH site only)
- Administer NPI-Q (AD patients only)
- Administer ADAS-Cog (AD patients only)
- Administer MoCA (AD patients only)
- Administer AROMHA olfactory battery
- Administer Since Last Visit C-SSRS questionnaire
- Administer End of Study Form
- Administer Global Impression of Change survey
    - Global Impression of Change surveys will be completed by the study participant, study partner (AD patients only) and clinician
- Perform survival assessment
- Collect blood sample for:
    - Clinical laboratory assessments, including Hematology (CBC with differential), Comprehensive Metabolic Panel with Liver Function Tests, Coagulation and a Lipid Panel.
    - Research (for PK, Biomarker analysis, Immune cell profiling and storage).
- Collect urine sample for:
    - Urinalysis
    - Urine Pregnancy Test (for WOCBP)
    - Future Research
- Perform study drug accountability and collect all unused drug and empty containers
- Review and document concomitant medications and therapies
- Assess and document AEs

Participants who withraw consent or early terminate from the study will be asked to complete a Final Safety Visit when they notify the site of their desire to end participation or as soon as possible thereafter. All the activities outlined above for the Week 24 Visit will be performed at a Final Safety Visit.

7.8 Follow-up Telephone Call

The Follow-up Telephone Call will take place 28 to 33 days after a participant's last dose of study drug. All participants will be asked to complete a Follow-up Telephone Call. Participants who withdraw consent will also be asked to complete the Follow-up Telephone Call if they were

still taking study drug within 28 days of their withdrawal, in addition to the Final Safety Visit. The following assessments will be collected:

- Review and document concomitant medications and therapies
- Assess and document AEs

7.9 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practice (GCP), or Manual of Procedures requirements. The noncompliance may be either on the part of the participant, the site investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

All deviations from the protocol must be addressed in the participant's source documents and will be tracked by the Monitoring team. All major protocol deviations will be sent to the single IRB.

7.10 Missed Visits and Procedures

Missed visits and any procedures not performed (not attempted) for reasons other than illness, injury or progressive disability (i.e. participant is physically unable to perform test) will be reported as protocol deviation.

Procedures or visits not performed due to illness, injury or disability, including procedures that were attempted but failed (i.e. blood samples unable to be drawn after multiple attempts, or weight unable to be obtained due to participant immobility) will not be reported as protocol deviations.

Study drug compliance that is outside the limits set in the study operations manual will be reported as a protocol deviation.

Details and specific instructions regarding protocol deviations, including any exceptions to this standard procedure, are found in the study operations manual.

7.11 COVID-19 Pandemic

COVID-19 Vaccination-It is strongly recommended that participants receive COVID-19 vaccinations before entering the trial as applicable per CDC/FDA guidelines. COVID-19 vaccinations received during the trial will be recorded in the EDC as concomitant medications. As there are two types of COVID-19 vaccinations available, live and non-live, Baricitinib use with live vaccine is not recommended.

- If a participant receives a COVID-19 vaccine prior to the trial, it must be received at least 14 days prior to the Screening Visit.
- If a participant receives a COVID-19 vaccine during the trial, it must be received at least 14 days prior to next LP visit.

COVID-19 Reporting -In the event that a study participant is diagnosed with COVID-19 infection, local health authority recommendations regarding treatment should be followed and the event should be reported as an AE/SAE depending on severity of infection and diagnosis.

COVID-19 Site Access Limitations-In the event the COVID-19 pandemic results in site closures or limited access to a study site, the site should contact the NCRI Coordination Center to review the impact on the visit schedule of enrolled participants. Assessments that can be done remotely may proceed as outlined in Section 7.0 of the protocol(Option for Remote Visits). The study team will be reviewing the impact of COVID-19 on an ongoing basis and will make updates to the study protocol as indicated.

8 CLINICAL ASSESSMENTS AND OUTCOME MEASURES

8.1 Clinical Variables

Assessments will be performed at designated time-points throughout the study for clinical evaluation. In addition to the assessments evaluated below, participants will provide information related to demographics, medical history, including ALS and AD diagnostic history, as well as concomitant medication usage.

8.1.1 Vital Signs, Weight & Height

Vital signs will be obtained after the participant has been in a seated position for several minutes. Vital signs, including systolic and diastolic blood pressure, pulse rate (radial artery)/minute, respiratory rate/minute, temperature and weight will be assessed at specified visits. Height will be measured and recorded at the Screening Visit only. Vital signs will not be collected at remote study visits.

8.1.2 Clinical Laboratory Assessments

The following laboratory tests will be performed for safety:

- Hematology with differential panel: complete blood count with differential (hematocrit, hemoglobin, platelet count, Red Blood Count (RBC) indices, Total RBC, Total White Blood Count (WBC), and WBC & differential).

- Comprehensive Metabolic Panel including Liver function tests (LFTs): alanine aminotransferase (ALT (SGPT)), aspartate aminotransferase (AST (SGOT)), albumin, alkaline phosphatase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, potassium, sodium, total bilirubin, total protein

- Magnesium and phosphate

- Coagulation: prothrombin time (PT), partial thromboplastin time (PTT) and international normalized ratio (INR).

- Urinalysis: bilirubin, blood, clarity, color, glucose, ketones, nitrate, pH, protein, specific gravity, urobilinogen and WBC screen.

- Urine pregnancy test for women of childbearing potential (WOCBP).

- Lipid panel: total cholesterol, triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL); assessed at the Baseline, Week 8 and Week 24 or Final Safety Visit.

- Vitamin B12, Thyroid Stimulating Hormone(TSH) and Folate; assessed at the Screening Visit only.

- HIV, Hepatitis B panel and Hepatitis C panel; assessed at the Screening Visit only.

- Tuberculosis testing (Quantiferon, T-SPOT, or skin test); assessed at the Screening Visit only.
    - If a participant travels to an endemic area over the course of the study, TB testing should be repeated.

All participants will have safety laboratory tests at all visits during the treatment period as outlined in the protocol. These samples will be analyzed at each site's local laboratory. For visits conducted remotely, safety lab collection may be performed and analyzed at a local lab facility. The SI may order additional testing, if needed, to further assess an AE, or if there is any suspicion that a participant may be pregnant, throughout the course of the study.

8.1.3 Blood draw for Pharmacokinetic and Biomarker Analysis

Pharmacokinetic Analysis
Participants will have blood drawn to assess baricitinib concentrations. At the Baseline Visit, the blood sample will be collected pre-dose. At Week 8,Week 16, and Week 24, the research blood sample will be collected 1 hour (± 10 minutes) post-dose and must be collected prior to the LP. Every attempt should be made to collect samples within the allotted timeframe. The time of drug administration and sample collection will be recorded.

Biomarker Analysis
Blood will also be collected for biomarker analysis, including (but not limited to) the following biomarkers: IL-6, CCL2, pPKR, PKR, pPKR/PKR ratio, CXCL10, IFNG and TAR DNA-binding protein 43 (TDP-43) levels and immune cell profiling in the plasma.

All samples will be labeled with a code. The code will not include any identifiable information.

Specific instructions regarding the collection, processing, storage and shipment of these samples will be provided in the Site Manual of Procedures (MOP).

Future Research
Remaining blood samples will be stored in a sample repository. Samples will be stored in biorepositories respective to their disease at MGH.These samples will be used for future research in motor neuron diseases. Any research performed on the samples is for research purposes only.

There is no scheduled date on which the samples will be destroyed. Samples may be stored for research until they are used, damaged, decayed or otherwise unfit for analysis.

8.1.4 Blood draw for Genetic Testing

All participants will provide a blood sample at the Baseline Visit for *C9ORF72* and *APOE* genetic testing, regardless of whether or not they have previously received testing for these genes. These

samples will be sent to Prevention Genetics for analysis. Study participants will have the option to learn the results of genetic testing. Both *C9ORF72* and *APOE* genetic test results will be returned to AD and ALS participants in the disclosure group. The study investigator will discuss genetic testing results and their implications with participants. If a participant decides not to learn results of genetic testing, they will be placed in the nondisclosure group. Results of genetic testing will not impact participation in the study.

Specific instructions regarding the collection, processing, storage and shipment of these samples will be provided in the Site Manual of Procedures (MOP).

8.1.5 Urine Sample for Future Research

All participants will provide a urine sample for storage in a biorepository at the following study visits: Baseline, Week 8, Week 16 and Week 24. Samples will be stored in biorepositories respective to their disease at MGH. These samples will be used for future research in motor neuron disease. Coded samples will be stored.

8.1.6 12-Lead Electrocardiogram (ECG)

A standard 12-lead ECG will be performed at the Screening Visit. Tracings will be reviewed locally. A copy of the tracings will be kept on site as part of the source documents.

8.1.7 Physical Examination

A physical examination will be performed at the Screening and Week 24 or Final Safety Visit. The following systems will be examined: head/neck, eyes, ears, nose/throat, cardiovascular, lungs, abdomen, musculoskeletal, central nervous system, extremities, and skin.

8.1.8 Neurological Examination

A neurological examination will be performed at the Screening and Week 24 or Final Safety Visit. Examination will include assessment of mental status, cranial nerves, motor and sensory function, reflexes, coordination, and stance/gait.

8.1.9 Columbia Suicide Severity Rating Scale (C-SSRS)

The US FDA recommends the use of a suicidality assessment instrument that maps to the Columbia Classification Algorithm for Suicide Assessment (C-CASA)(19). The C-CASA was developed to assist the FDA in coding suicidality data accumulated during the conduct of clinical trials of antidepressant drugs. One such assessment instrument is the Columbia Suicide Severity Rating Scale (C-SSRS)(20-21). The C-SSRS involves a series of probing questions to inquire about possible suicidal thinking and behavior.

At the Screening Visit, the C-SSRS Baseline version will be administered. This version is used to assess suicidality over the participant's lifetime and specifically for the previous 6-month time period.

At all clinic visits after the Screening Visit, the Since Last Visit version of the C-SSRS will be administered at study sites. This version of the scale assesses suicidality since the participant's last visit.

If there is a positive response to question 4 or 5 on the severity of ideation subscale or any positive response on the suicidal behavior subscale of suicide attempt or suicidal ideation by the participant during the administration of the C-SSRS during the treatment period, the appropriately qualified clinician will be notified during the study visit to determine the appropriate actions required to ensure the participant's safety. The site must ensure that the participant is seen by a licensed physician (or other qualified individual as required by local institutional policy) before leaving the study site. The investigator will determine whether the participant should remain on study drug. Reference to the Clinical Triage Guidelines Using the C-SSRS can be found here https://cssrs.columbia.edu/wp-content/uploads/C-SSRStriageexampleguidelines.pdf.

It is recommended that a medically licensed physician, nurse, nurse practitioner, or physician assistant to assess suicidality with the C-SSRS. All evaluators must be certified to perform the C-SSRS; specific certification requirements are outlined in the site MOP. Certification is required prior to performing the C-SSRS.

8.1.10 Lumbar Puncture for CSF Collection

LPs will be performed and CSF will be collected. If a standard LP cannot be performed, a fluoroscopic LP may be done instead. LPs will be performed at Screening, Baseline, Week 8 and Week 16. CBC and coagulation lab results must be reviewed prior to performing study LPs. Sites should follow their local lumbar puncture procedure policies for performing LPs. The performing clinician will make a maximum of 2 lumbar puncture attempts. Please refer to Study MOP for more information.

At the Baseline Visit, the LP must be performed pre-dose. At Week 8 and Week 16, the LP must occur after the research blood draw and within 2 to 4 hours after dosing (ideally 2 hours post-dose). The Site Investigator (SI) will discuss all potential LP risks to the participants including:

- Local pain at injection site;
- Reaction to anesthetic agents;
- Bleeding at needle entrance site;
- Infection at needle entrance site; and,
- Post-LP low-pressure headache.

The procedure must be performed by the SI or another licensed practitioner with experience and training in performing LPs, and is listed on the site delegation log.

A thorough review of medical history, a physical exam, and evaluation of lab results as outlined in LP policies for each site will allow trained clinicians to make a clinical determination regarding the safety of performing a LP to access spinal fluid. The clinician will make a maximum of two attempts to perform a LP. Standard LPs will be performed in clinic. The determination on whether fluoroscopy is needed will be made either before or after a LP attempt without fluoroscopy. For

participants who have known challenging back anatomy or prior experience with a LP that resulted in the procedure being done under fluoroscopy, the decision may be made to go directly to fluoroscopic LP with no standard LP attempt. For the vast majority of participants, the decision will only be made following an unsuccessful standard LP attempt. Fluroscopy guided LPs will be performed by interventional radiology service, not by study team members.

A maximum of 20cc of CSF will be collected at each LP visit for pharmacokinetic and biomarker analysis. Biomarker assays will include inflammatory biomarkers (CCL2, CXCL10, pPKR, PKR, pPKR/PKR ratio, IL-6 and IFNG) and neuronal death biomarkers (NfL, tau and phospho-tau). Instructions for labeling, processing, and shipping CSF are detailed in the Manual of Operations.

Remaining CSF samples will be stored in a sample repository. Samples will be stored in biorepositories respective to their disease at MGH. These samples will be used for future research in motor neuron diseases. All samples will be labeled with a code. The code will not include any identifiable information.

There is no scheduled date on which the samples will be destroyed. Samples may be stored for research until they are used, damaged, decayed or otherwise unfit for analysis.

8.1.11 Adverse Events

Adverse events (AEs) will be documented at each study visit, including the Screening Visit once the informed consent form has been signed by the participant, and at all study visits, including the Follow-up Telephone call 28 to 33 days after the last dose of study drug. Information on adverse effects of study medication and on inter-current events will be determined at each visit by direct questioning of the participants, review of concomitant medications, and vital sign results.

8.2 Outcome Measures

8.2.1 Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R)

The ALSFRS-R is a quickly administered (5 minutes) ordinal rating scale (ratings 0-4) used to determine participants' assessment of their capability and independence in 12 functional activities(22). All 12 activities are relevant in ALS. Initial validity was established by documenting that in ALS patients, change in ALSFRS-R scores correlated with change in strength over time, was closely associated with quality of life measures, and predicted survival. The test-retest reliability is greater than 0.88 for all test items. The advantages of the ALSFRS-R are that the categories are relevant to ALS, it is a sensitive and reliable tool for assessing activities of daily living function in those with ALS, and it is quickly administered. With appropriate training the ALSFRS-R can be administered with high inter-rater reliability and test-retest reliability. The ALSFRS-R can be administered by phone with good inter-rater and test-retest reliability. The equivalency of phone versus in-person testing, and the equivalency of study participant versus caregiver responses have also recently been established. Therefore, if necessary, the ALSFRS-R may be given to the study participant over the phone. All ALSFRS-R evaluators must complete training to perform this assessment.

8.2.2 Pulmonary Function Testing- Slow Vital Capacity (SVC)

Slow Vital Capacity (SVC): The vital capacity (VC) (percent of predicted normal) will be determined, using the upright slow VC method. The VC can be measured using conventional spirometers that have had a calibration check prior to participant testing. A printout from the spirometer of all VC trials will be retained. All VC evaluators must complete training to perform this assessment. Three VC trials are required for each testing session, however up to 5 trials may be performed if the variability between the highest and second highest VC is 10% or greater for the first 3 trials. Only the 3 best trials are recorded on the CRF.

SVC is not required to determine eligibility; however, it is required to be collected at the Screening Visit and Week 24 or Final Safety Visit. Every attempt should be made to perform SVC at required visits. If SVC cannot be performed in clinic due to pandemic-related restrictions at study center, SVC or Forced Vital Capacity (FVC) can be performed in a dedicated pulmonary function lab. Collection of SVC is optional at the Baseline and Week 8.

8.2.3 Cognitive Evaluations

Cognitive testing will include evaluations of the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) and the Montreal Cognitive Assessment (MoCA) in participants with AD.

The ADAS-Cog is validated and widely used as a primary cognitive outcome measure in AD pharmacotherapy studies. This is a psychometric instrument that evaluates memory (immediate and delayed word recall, word recognition), attention (number cancellation), reasoning (following commands), language (naming, comprehension), orientation, ideational praxis (placing letter in envelope) and constructional praxis (copying geometric designs), and executive functioning (maze completion). Scoring is in the range of 0 to 90 with a higher score indicating greater impairment(23). This test will be administered by experienced raters at each site at Baseline and Week 24 or Final Safety Visit.

The Montreal Cognitive Assessment (MoCA) is commonly utilized questionnaire in clinical trials and research settings to measure levels of cognitive impairment. The MoCA measures five areas of cognitive function: orientation, visuospatial, attention and calculation, recall, and language(24). The MoCA will take approximately 10 minutes to complete. The test will be administered by experienced raters at each site at Screening and Week 24 or Final Safety Visit. There are 3 available versions(8.1, 8.2, 8.3). Participants should be given MoCA Version 8.1 at the Screening Visit and MoCA Version 8.2 at the Week 24 visit as long as they have NOT received the same MoCA version clinically within the last 3 months. The MoCA version used at a study visit should be accurately documented in Source Document and within the EDC for each visit.

The NIH Toolbox® is a multi-dimensional set of brief measures to assess cognitive, sensory, motor and emotional function that can be administered in 2 hours or less across diverse study designs and settings. The NIH Toolbox contains two types of measures: performance based tests of function and self-report and proxy measures(primarily for emotion). The NIH Toolbox

measures are available for easy administration using an iPad app. The test will be administered by experienced raters at each site at Baseline and Week 24 or Final Safety Visit.

8.2.4 Neuropsychiatric Inventory Questionnaire (NPI-Q)

The Neuropsychiatric Inventory (NPI) measures dementia-related behavioral symptoms and is used to assess changes in psychological status. There are several versions of the NPI including the NPI-Questionnaire (NPI-Q), NPI-Clinician (NPI-C) and the NPI-Nursing Home (NPI-NH). All examine 12 sub-domains of behavioral functioning including: hallucinations, delusions, agitation, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability, aberrant motor activity, eating abnormalities, and night-time behavioral alternations(25). The NPI-Q is completed by a trained rater through interview with the participant's study partner. It is well-validated and extensively used in clinical trials in AD. The NPI-Q will be administered at the Baseline and Week 24 or Final Safety Visit.

8.2.5 Accessible Remote Olfactory Mediated Health Assessments (AROMHA) olfactory battery

The AROMHA olfactory battery, a measure of cognitive processing of odor stimuli, is comprised of odor percept identification (OPID-9; OPID-18), episodic memory of odor percepts (POEM), and an odor discrimination (OD) test. These tests quantify cognitive processing of olfactory stimuli, which has been shown to be affected in preclinical and clinical AD(26). The test is administered by a trained research coordinator and takes about 30 minutes to complete. AROMHA olfactory battery will be administered at the Baseline and Week 24 or Final Visit for patients with AD and ALS and asymptomatic carriers of ALS causative genes. If assessment is not performed due to COVID-related concerns, it will not be considered a protocol deviation.

8.2.6 Survival Assessment

Survival endpoint will be considered as mortality or initiation of permanent assisted ventilation. Study staff may contact participants or their caregivers or reference clinical records after a participant completes follow-up in order to determine long-term vital status.

8.2.7 End of Study Form

An End of Study Form will be completed by participants at the Week 24 or Final Safety Visit. This will include questions regarding overall experience with the trial.

8.2.8 Global Impression of Change Survey

A global impression of change survey will be completed by the study participant, study partner (for AD participants only) and the treating investigator. This survey will be completed at the final study visit to assess changes to the participant’s overall status since the start of the study.

8.2.9 Training and Validation

Training will be completed to administer the C-SSRS, NPI-Q, MoCA, ALSFRS-R, SVC, and AROMHA olfactory battery tests. It is strongly preferred that a single evaluator performs all measures throughout the study, if possible. Please refer to the Site MOP for a more detailed description of the training and certification required for the outcome assessments.

8.3 Study Partners (AD Participants only)

For participants with major neurocognitive disorder, a study partner must accompany the participant to every study visit. For participants with mild neurocognitive disorder or subjective cognitive decline, a study partner must be available to participate in the following study visits: Baseline, and Week 24.

The study partner will be asked to sign the study partner consent form prior to study participation and complete forms including the NPI-Q and Global Impression of Changes Survey. While it is preferred that study partners complete the NPI-Q and Global Impression of change survey in clinic, these assessments may be completed remotely.

9 SAFETY AND ADVERSE EVENTS

The adverse event definitions and reporting procedures provided in this protocol comply with all applicable United States Food and Drug Administration (FDA) regulations and International Council for Harmonisation (ICH) guidelines. The Site Investigator will carefully monitor each participant throughout the study for possible adverse events. All AEs will be documented on CRFs designed specifically for this purpose. It is also important to report all AEs, especially those that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

9.1 Definitions of AEs, Suspected Adverse Drug Reactions & SAEs

9.1.1 Adverse Event and Suspected Adverse Drug Reactions

An adverse event is any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with a study, use of a drug product or device whether or not considered related to the drug product or device.

Adverse drug reactions (ADR) are all noxious and unintended responses to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. Therefore, a subset of AEs can be classified as suspected ADRs, if there is a causal relationship to the medicinal product.

Examples of adverse events include: new conditions, worsening of pre-existing conditions, clinically significant abnormal physical examination signs (i.e. skin rash, peripheral edema, etc), or clinically significant abnormal test results (i.e. lab values or vital signs), with the exception of outcome measure results, which are not being recorded as adverse events in this trial (they are being collected, but analyzed separately). Stable chronic conditions (i.e., diabetes, arthritis) that are present prior to the start of the study and do not worsen during the trial are NOT considered adverse events. Chronic conditions that occur more frequently (for intermittent conditions) or with greater severity, would be considered as worsened and therefore would be recorded as adverse events.

Adverse events are generally detected in two ways:

Clinical → symptoms reported by the participant or signs detected on examination.

Ancillary Tests → abnormalities of vital signs, laboratory tests, and other diagnostic procedures (other than the outcome measures, the results of which are not being captured as AEs).

For the purposes of this study, clinically noteworthy progression/worsening of cognitive, behavioral or functional abilities beyond those expected by natural history of the disease or syndrome should be recorded as AEs.

The following measures of disease progression for ALS will not be recorded as AE even if they worsen (they are being recorded and analyzed separately): vital capacity results and ALSFRS-R results.

The following measures of disease progression for AD will not be recorded as AEs even if they worsen(they are being recorded and analyzed separately): ADAS-Cog and AROMHA olfactory battery.

If discernible at the time of completing the AE log, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Site Investigator and recorded on the AE log. However, if an observed or reported sign, symptom, or clinically significant laboratory anomaly is not considered by the Site Investigator to be a component of a specific disease or syndrome, then it should be recorded as a separate AE on the AE log. Clinically significant laboratory abnormalities, such as those that require intervention, are those that are identified as such by the Site Investigator.

Participants will be monitored for adverse events from the time they sign consent until completion of their participation in the study (defined as death, consent withdrawal, loss to follow up, early study termination for other reasons or following completion of the entire study).

An unexpected adverse event is any adverse event, the specificity or severity of which is not consistent with the current package insert. An unexpected, suspected adverse drug reaction is any unexpected adverse event that, in the opinion of the Site Investigator or Sponsor, there is a reasonable possibility that the investigational product caused the event.

9.1.2 Serious Adverse Events

A serious adverse event (SAE) is defined as an adverse event that meets any of the following criteria:

1. Results in death.
2. Is life threatening: that is, poses an immediate risk of death as the event occurred.
    a. This serious criterion applies if the study participant, in the view of the Site Investigator or Sponsor, is at immediate risk of death from the AE as it occurs. It does not apply if an AE hypothetically might have caused death if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
    a. Hospitalization for an elective procedure (including elective PEG tube/g-tube/feeding tube placement) or a routinely scheduled treatment is not an SAE by this criterion because an elective or scheduled “procedure” or a “treatment” is not an untoward medical occurrence.
4. Results in persistent or significant disability or incapacity.

a. This serious criterion applies if the “disability” caused by the reported AE results in a substantial disruption of the participant’s ability to carry out normal life functions.

5. Results in congenital anomaly or birth defect in the offspring of the participant (whether the participant is male or female).
6. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.
7. Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An inpatient hospital admission in the absence of a precipitating, treatment-emergent, clinical adverse event may meet criteria for "seriousness" but is not an adverse experience, and will therefore, not be considered an SAE. An example of this would include a social admission (participant admitted for other reasons than medical, e.g., lives far from the hospital, has no place to sleep).

A serious, suspected adverse drug reaction is an SAE that, in the opinion of the Site Investigator or Sponsor, there is a reasonable possibility that the investigational product caused the event.

The Site Investigator is responsible for classifying adverse events as serious or non-serious.

9.2 Assessment and Recording of Adverse Events

The Site Investigator will carefully monitor each participant throughout the study for possible AEs. All AEs will be documented on CRFs designed specifically for this purpose. All AEs will be collected and reported in the electronic data capture (EDC) system and compiled into reports for periodic reviewing by the Medical Monitor. The Medical Monitor shall promptly review all information relevant to the safety of the investigational product, including all serious adverse events (SAEs). Special attention will be paid to those that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

9.2.1 Assessment of Adverse Events

At each visit (including telephone interviews), the participant will be asked if they have had any problems or symptoms since their last visit in order to determine the occurrence of adverse events. If the participant reports an adverse event, the Investigator will probe further to determine:

1. Type of event
2. Date of onset and resolution (duration)
3. Severity (mild, moderate, severe)
4. Seriousness (does the event meet the above definition for an SAE)
5. Causality, relation to investigational product and disease

6. Action taken regarding investigational product
7. Outcome

9.2.2 Relatedness of Adverse Event to Investigational Product

The relationship of the AE to the investigational product should be specified by the Site Investigator, using the following definitions:

1. Not Related:	Concomitant illness, accident or event with no reasonable association with treatment.
2. Unlikely:	The reaction has little or no temporal sequence from administration of the investigational product, and/or a more likely alternative etiology exists.
3. Possibly Related:	The reaction follows a reasonably temporal sequence from administration of the investigational product and follows a known response pattern to the suspected investigational product; the reaction could have been produced by the investigational product or could have been produced by the participant's clinical state or by other modes of therapy administered to the participant. (Suspected ADR)
4. Probably Related:	The reaction follows a reasonably temporal sequence from administration of investigational product; is confirmed by discontinuation of the investigational product or by re-challenge; and cannot be reasonably explained by the known characteristics of the participant's clinical state. (Suspected ADR)
5. Definitely Related:	The reaction follows a reasonable temporal sequence from administration of investigational product; that follows a known or expected response pattern to the investigational product; and that is confirmed by improvement on stopping or reducing the dosage of the investigational product, and reappearance of the reaction on repeated exposure. (Suspected ADR)

9.2.3 Recording of Adverse Events

All clinical adverse events are recorded in the AE Log in the participant's study binder. The site is instructed to fill out the AE Log and enter the AE information into the EDC system within 5 business days of the site learning of a new AE or receiving an update on an existing AE.

Please Note: Serious Adverse Events (SAEs) must be reported to the MGH Coordination Center within 24 hours of the site learning of the SAE.

Entries on the AE Log (and into the EDC) will include the following: name and severity of the event, the date of onset, the date of resolution, relationship to investigational product, action taken, and primary outcome of event.

9.3 Adverse Events and Serious Adverse Events - Reportable Events

The following are considered reportable events and must be reported to the MGH Coordination Center within 24 hours of the site being notified of the event.

- All events that meet the above criteria for Serious Adverse Events (SAEs)
- Any pregnancy
- Dosage Changes (Dose Management)
  - Investigational Product Suspension, Reduction or Re-challenge
  - Investigational Product Discontinuation

9.4 Reportable Medical Procedures

The following are medically indicated procedures and should be reported in the EDC.

- Feeding Tube Placement
- Permanent Assisted Ventilation (PAV)*
- Tracheostomy

* Permanent Assisted Ventilation (PAV) is defined as more than 22 hours daily of non-invasive mechanical ventilation for more than one week (7 days). The date of onset of PAV is the first day of the seven days.

9.5 Data and Safety Monitoring

An independent Data and Safety Monitoring Board (DSMB) will be assembled for the trial. A DSMB Charter will detail the processes of this group. The DSMB will receive unblinded reports summarizing recruitment, protocol compliance, the frequency of all clinical adverse events and safety laboratory tests at planned periodic meetings as specified in the DSMB charter. The DSMB Chair may call ad hoc meetings. Meetings will be held via teleconference.

The DSMB will review safety data throughout the trial. Serious infections, cancer diagnoses, and thrombotic events occurring within 24 hours of dosing, and any severe unexpected serious adverse events are considered events of interest and will be reported in real-time (within 1 business day of Coordination Center (CC) awareness) to the DSMB. The DSMB can ask to receive the SAE reports more frequently. Any death will lead to prompt review by the DSMB. Two or more of the same SAE deemed probably or definitely related to study drug or one death in the treatment group deemed probably or definitely related to study drug will lead to prompt review by the DSMB and consideration of any required modification, suspension, or termination. Recommendations for modification, suspension, or termination of the trial based on safety data will be made by the DSMB to the PI and Steering Committee. A notable increase in the frequency of any adverse event

should be examined by the DSMB although it may not lead to a recommendation by the DSMB. The DSMB may stop the trial for safety if they determine that the risk of study participation is greater than the possible benefit of the study drug.

The NCRI CC will be responsible for communication with the DSMB.

Complete information can be found in the Data and Safety Monitoring Charter.

10 STATISTICAL CONSIDERATIONS

10.1 Sample Size and Power Calculations

10.1.1 Interim Analyses and Early Stopping for Futility

The trial will enroll a minimum of 10 participants. If none of the first 10 participants meets either the PK or PD criterion for continued enrollment based on CSF collected at the 8- and 16-week LPs, then the trial will be stopped early for futility. The trial has an 80% probability of stopping early for futility if the expected percentage of participants meeting either the PK or PD criterion is less than 2.2%. The trial has only a 5% probability of stopping early for futility if the expected percentage of participants meeting either the PK or PD criterion is at least 26%.

10.1.2 Pharmacodynamics

If the trial completes enrollment of all 20 participants, we will have 80% power to detect a decline in CCL2 levels in the CSF from pre-treatment to post-treatment if the expected decline is at least 0.66 SD based on two-tailed testing at $p < 0.05$ for this primary measure of target engagement. For the 10 additional secondary biomarkers of inflammation and neuronal death, each tested at two-sided $p < 0.004$ to control for multiple comparisons, the study will have 80% power to detect a decline from pre-treatment to post-treatment in any one of the biomarkers if the expected decline is at least 0.94 SD. To detect changes in CCL2 levels in the CSF or changes in the secondary biomarkers only among the 10 AD or 10 ALS participants separately, the minimum expected changes detectable with 80% power when testing at two-tailed $p < 0.025$ or $p < 0.002$ are 1.14 SD and 1.70 SD, respectively. The trial will have 80% power to detect correlations between the concentration of baricitinib in the CSF and the concentration of any one of the 11 primary and secondary biomarkers if the true correlation is at least 0.71.

10.1.3 Safety

With either 10 or 20 participants enrolled and exposed to baricitinib, the trial will have an 80% probability of observing at least one instance of a given type of adverse experience if the expected percentage of participants experiencing such an event is at least 15% and 7.7%, respectively.

10.2 Analysis Populations

Analyses of both safety and pharmacodynamics will include all participants exposed to baricitinib. Primary analyses of pharmacokinetics and pharmacodynamics will censor follow-up at the time that participants discontinue study drug, although participants who discontinue study drug early will continue to be followed under the normal schedule of assessments if they are willing. Changes in pharmacodynamic measures after discontinuation of study drug will be informative of the persistence of any observed pharmacodynamic response.

10.3 Pharmacokinetics

Levels of baricitinib in the CSF will be presented as visit-specific means and standard deviations and analyzed in a linear mixed model that includes diagnosis (two levels: AD and ALS), visit (four levels: screening, baseline, week 8, and week 16), and their interaction as fixed effects and unstructured within-person covariance among repeated measures. The primary estimate will be a linear contrast of least-square means estimating the mean within-participant change from baseline to the average of weeks 8 and 16, averaged across AD and ALS participants. Additional linear contrasts will be used to test for differences between AD and ALS participants and between levels at weeks 8 and 16.

10.4 Pharmacodynamics

Levels of CCL2 in the CSF and of the secondary biomarkers of inflammation and neuronal death will be presented as visit-specific means and standard deviations and analyzed in the same linear mixed model used for analyzing baricitinib levels. Biomarker levels will be log transformed prior to analysis if distributions are right skewed. The primary estimate will be a linear contrast of least-square means testing whether the within-participant change from baseline to week 8 is greater than the within-participant change from screening to baseline, averaged across AD and ALS participants. Additional linear contrasts will be used to test for change from baseline to week 16 and for differences between AD and ALS participants.

Pearson or Spearman correlations, depending on approximate normality of original or transformed values, will be calculated between levels of baricitinib in the CSF at week 8 and change in levels of pharmacodynamic biomarkers from baseline to week 8, both overall and among AD and ALS participants separately. The same calculations will be performed for levels and changes over 16 weeks.

10.5 Safety

Safety will be assessed by the occurrence of treatment-emergent adverse events , treatment-emergent serious adverse events , and treatment-emergent clinically significant abnormalities in clinical and laboratory values both overall and among AD and ALS participants separately. AEs will be coded to system organ class and preferred terms from a consistent version of the MedDRA library and summarized as counts of events and proportions of participants experiencing a given type of event. The distribution of severity, relationship to the study intervention, action taken with respect to study intervention, and outcome of all TEAEs will be tabulated. The rate of adverse effects in trial participants will be compared to the frequency of adverse effects documented in the package insert to determine the safety of baricitinib in AD and ALS patients relative to rheumatoid arthritis patients. We hypothesize that the safety profile in AD and ALS patients will be within the expected profile reported for patients taking baricitinib for its primary indication, rheumatoid arthritis.

10.6 Missing Data

This trial will not be intent to treat. Participants who do not initiate baricitinib will not be included in analyses and observations made after discontinuation of study drug early will be excluded from

the primary analyses. Potential bias from otherwise informative missingness due to loss to follow-up will be minimized through use of mixed models that include all participants who initiate study drug and implicitly impute missing data based on the observed within-person covariance among repeated measures.

11 DATA COLLECTION, MANAGEMENT AND MONITORING

11.1 Role of Data Management

Data Management (DM) is the development, execution and supervision of plans, policies, programs, and practices that control, protect, deliver, and enhance the value of data and information assets.

All data will be managed in compliance with Everest policies and applicable NCRI and regulatory requirements. Site personnel will collect, transcribe, correct, and transmit the data onto source documents, Case Report Forms (CRFs), and other forms used to report, track and record clinical research data. Clinical sites will be monitored to ensure compliance with data management requirements and Good Clinical Practices. DM is responsible for developing, testing, and managing clinical data management activities.

11.1.1 Data Entry and Checks

The site personnel are strongly advised to enter information into the Electronic Data Capture (EDC) System within 5 days of a visit. Data collection is the responsibility of the staff at the site under the supervision of the SI. During the study, the SI must maintain complete and accurate documentation for the study.

The EDC includes password protection. An edit checking and data clarification process will be put in place to ensure accuracy and completeness of the database. Logic and range checks as well as more sophisticated rules will be built into the EDC to provide immediate error checking of the data entered. The system has the capability to automatically create electronic queries for forms that contain data that are out of range, out of window, missing or not calculated correctly. The sites will only have access to the queries concerning their participants.

11.1.2 Data Lock Process

The application will have the ability to lock the database to prevent any modification of data once the study is closed. Once this option is activated, every user will have Read-Only access to the data. The database can only be locked after each SI has signed off on their participants and all queries have been resolved.

11.1.3 Quality Assurance

Protocol procedures are reviewed with the SI and associated personnel prior to the study to ensure the accuracy and reliability of data. Each SI must adhere to the protocol detailed in this document and agree that any changes to the protocol must be approved by the Coordination Center prior and sIRB. Each SI will be responsible for enrolling only those study participants who have met protocol eligibility criteria.

11.2 Clinical Monitoring

Study Monitors conduct remote and will visit each study site (if deemed safe with regards to travel) to review source documentation materials, informed consent forms, and confirm entered data and that data queries have been accurately completed, and again at a study close-out visit. Study Monitors will also verify that SAEs and protocol deviations have been reported appropriately, as required. The Study Monitors will also review clinical facilities, resources and procedures for evaluating study participants and study drug dispensing. Subsequently, the Study Monitors will provide monitoring reports to the NCRI Project Manager and, if requested, will provide reports of protocol compliance to the Study Principal Investigator and the Steering Committee. Completed informed consent forms from each participant must be available in the participant's file and verified for proper documentation. A document outlining the monitoring plan is provided to each Study Monitor.

11.3 Data Handling and Record Keeping

The SI is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Dark ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. Do not erase, overwrite, or use correction fluid or tape on the original.

Source document templates (SDTs) will be provided for use and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents and discrepancies should be explained. The Coordination Center and Study Monitors will provide guidance to SIs on making corrections to the source documents and eCRFs.

11.3.1 Confidentiality

Study participant medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited. Upon the participant's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. All local and federal guidelines and regulations regarding maintaining study participant confidentiality of data will be adhered to.

Data generated by this study must be available for inspection by representatives of the US FDA, the Office for Human Research Protections (OHRP), the sponsor, all pertinent national and local health and regulatory authorities, the Coordination Center or their representative, Study Monitoring personnel, and the IRBs.

11.3.2 Study Discontinuation

The study can be terminated at any time. Reasons for terminating the study may include the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to study participants.

- Study participant enrollment is unsatisfactory.
- Data recording is inaccurate or incomplete.
- Sponsor withdraws funding.

11.3.3 Retention of Records

US FDA regulations (21 CFR 312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs (if applicable), consent forms, laboratory test results, and medical inventory records, must be retained by the Site Investigator (SI) for two years after marketing application approval. If no application is filed, these records must be kept for two years after the investigation is discontinued and the US FDA and the applicable national and local health authorities are notified. The Coordination Center or their representative will notify the Site Investigators of these events. The Site Investigators should retain all study documents and records until they are notified in writing by the Sponsor or their representative.

11.3.4 Publications

The Principal Investigator, Mark Albers, will be responsible for publications of results from this trial. Co-authors will have the opportunity to review data and participate in the manuscript preparation. The responsibilities will include the following:

- Analyze and interpret data gathered in this study and write publications from these data.
- Submit manuscripts to selected journals and address peer reviewers' comments.
- Submit abstracts to selected meetings and present data at the meetings.
- Determine authorship on the basis of the Uniform Requirements for Manuscripts.

12 LITERATURE REFERENCES

1. Huang F, Zhu Y, Hsiao-Nakamoto J, et al. Longitudinal biomarkers in amyotrophic lateral sclerosis. *Ann Clin Transl Neurol*. 2020;7(7):1103-1116. doi:10.1002/acn3.51078
2. Galimberti D, Schoonenboom N, Scheltens P, et al. Intrathecal chemokine synthesis in mild cognitive impairment and Alzheimer disease. *Arch Neurol.* 2006;63(4):538-543.
3. Cai Q, Xin Z, Zuo L, Li F, Liu B. Alzheimer's Disease and Rheumatoid Arthritis: A Mendelian Randomization Study. Front Neurosci. 2018;12:627. Published 2018 Sep 12. doi:10.3389/fnins.2018.00627
4. Policicchio S, Ahmad AN, Powell JF, Proitsi P. Rheumatoid arthritis and risk for Alzheimer's disease: a systematic review and meta-analysis and a Mendelian Randomization study. Sci Rep. 2017;7(1):12861. Published 2017 Oct 9. doi:10.1038/s41598-017-13168-8
5. Kao LT, Kang JH, Lin HC, Huang CC, Lee HC, Chung SD. Rheumatoid Arthritis Was Negatively Associated with Alzheimer's Disease: A Population-Based Case-Control Study. PLoS One. 2016;11(12):e0168106. Published 2016 Dec 20. doi:10.1371/journal.pone.0168106
6. Judge A, Garriga C, Arden NK, et al. Protective effect of antirheumatic drugs on dementia in rheumatoid arthritis patients. Alzheimers Dement (N Y). 2017;3(4):612-621. Published 2017 Nov 9. doi:10.1016/j.trci.2017.10.002
7. Chou RC, Kane M, Ghimire S, Gautam S, Gui J. Treatment for Rheumatoid Arthritis and Risk of Alzheimer's Disease: A Nested Case-Control Analysis. CNS Drugs. 2016;30(11):1111-1120. doi:10.1007/s40263-016-0374-z
8. Rodriguez S, Sahin A, Schrank BR, et al. Genome-encoded cytoplasmic double-stranded RNAs, found in C9ORF72 ALS-FTD brain, propagate neuronal loss. Sci Transl Med. 2021;13(601):eaaz4699. doi:10.1126/scitranslmed.aaz4699
9. Rodriguez S, Hug C, Todorov P, et al. Machine learning identifies candidates for drug repurposing in Alzheimer's disease. *Nat Commun*. 2021;12(1):1033. Published 2021 Feb 15. doi:10.1038/s41467-021-21330-0
10. Kothur K, Bandodkar S, Chu S, et al. An open-label trial of JAK 1/2 blockade in progressive *IFIH1*-associated neuroinflammation. *Neurology*. 2018;90(6):289-291. doi:10.1212/WNL.0000000000004921
11. Shi JG, Chen X, Lee F, et al. The pharmacokinetics, pharmacodynamics, and safety of baricitinib, an oral JAK 1/2 inhibitor, in healthy volunteers. *J Clin Pharmacol*. 2014;54(12):1354-1361. doi:10.1002/jcph.354
12. Hoang TN, Pino M, Boddapati AK, et al. Baricitinib treatment resolves lower-airway macrophage inflammation and neutrophil recruitment in SARS-CoV-2-infected rhesus macaques. *Cell*. 2021;184(2):460-475.e21. doi:10.1016/j.cell.2020.11.007
13. Jorgensen SCJ, Tse CLY, Burry L, Dresser LD. Baricitinib: A Review of Pharmacology, Safety, and Emerging Clinical Experience in COVID-19. *Pharmacotherapy*. 2020;40(8):843-856. doi:10.1002/phar.2438
14. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. *N Engl J Med*. 2021;384(9):795-807. doi:10.1056/NEJMoa2031994

15. Mouton-Liger F, Paquet C, Dumurgier J, et al. Increased cerebrospinal fluid levels of double-stranded RNA-dependant protein kinase in Alzheimer's disease. *Biol Psychiatry*. 2012;71(9):829-835. doi:10.1016/j.biopsych.2011.11.031
16. Olumiant (baricitinib) Package Insert; URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/207924s000lbl.pdf
17. Zetterberg H, Tullhög K, Hansson O, Minthon L, Londos E, Blennow K. Low incidence of post-lumbar puncture headache in 1,089 consecutive memory clinic patients. *Eur Neurol.* 2010;63(6):326-330.
18. Quinn C, Macklin EA, Atassi N, et al. Post-lumbar puncture headache is reduced with use of atraumatic needles in ALS. *Amyotroph Lateral Scler Frontotemporal Degener.* 2013;14(7-8):632-634.
19. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry.* 2007;164(7):1035-1043
20. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. 2011;168(12):1266-1277. doi:10.1176/appi.ajp.2011.10111704
21. September 2010 US FDA Draft Guidance for Industry Suicidality: Prospective Assessment of Occurrence in Clinical Trials
22. Cedarbaum JM, Stambler N, Malta E, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). *J Neurol Sci*. 1999;169(1-2):13-21. doi:10.1016/s0022-510x(99)00210-5
23. Graham DP, Cully JA, Snow AL, Massman P, Doody R. The Alzheimer's Disease Assessment Scale-Cognitive subscale: normative data for older adult controls. *Alzheimer Dis Assoc Disord*. 2004;18(4):236-240.
24. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment [published correction appears in J Am Geriatr Soc. 2019 Sep;67(9):1991]. *J Am Geriatr Soc*. 2005;53(4):695-699. doi:10.1111/j.1532-5415.2005.53221.x
25. Kaufer DI, Cummings JL, Ketchel P, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *J Neuropsychiatry Clin Neurosci*. 2000;12(2):233-239. doi:10.1176/jnp.12.2.233
26. Dhilla Albers A, Asafu-Adjei J, Delaney MK, et al. Episodic memory of odors stratifies Alzheimer biomarkers in normal elderly. *Ann Neurol.* 2016;80(6):846-857.

13 APPENDICES

Appendix I: El Escorial World Federation of Neurology Criteria for the Diagnosis of ALS

Information obtained from the web site: ***www.wfnals.org***.

The diagnosis of Amyotrophic Lateral Sclerosis [ALS] requires:

A - The presence of:

(A:1) evidence of lower motor neuron (LMN) degeneration by clinical, electrophysiology cal or neuropathologic examination,

(A:2) evidence of upper motor neuron (UMN) degeneration by clinical examination, and

(A:3) progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination, together with

B - The absence of:

(B:1) electrophysiological and pathological evidence of other disease processes that might explain the signs of LMN and/or UMN degeneration, and

(B:2) neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs.

CLINICAL STUDIES IN THE DIAGNOSIS OF ALS

A careful history, physical and neurological examination must search for clinical evidence of UMN and LMN signs in four regions [brainstem, cervical, thoracic, or lumbosacral spinal cord] (see Table 1) of the central nervous system [CNS]. Ancillary tests should be reasonably applied, as clinically indicated, to exclude other disease processes. These should include electrodiagnostic, neurophysiological, neuroimaging and clinical laboratory studies. Clinical evidence of LMN and UMN degeneration is required for the diagnosis of ALS. The clinical diagnosis of ALS, without pathological confirmation, may be categorized into various levels of certainty by clinical assessment alone depending on the presence of UMN and LMN signs together in the same topographical anatomic region in either the brainstem [bulbar cranial motor neurons], cervical, thoracic, or lumbosacral spinal cord [anterior horn motor neurons]. The terms Clinical Definite ALS and Clinically Probable ALS are used to describe these categories of clinical diagnostic certainty on clinical criteria alone:

A. Clinically Definite ALS is defined on clinical evidence alone by the presence of UMN, as well as LMN signs, in three regions.

B. Clinically Probable ALS is defined on clinical evidence alone by UMN and LMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs.

C. Clinically Probable ALS - Laboratory-supported is defined when clinical signs of UMN and LMN dysfunction are in only one region, or when UMN signs alone are present in one region, and

LMN signs defined by EMG criteria are present in at least two limbs, with proper application of neuroimaging and clinical laboratory protocols to exclude other causes.

D. Clinically Possible ALS is defined when clinical signs of UMN and LMN dysfunction are found together in only one region or UMN signs are found alone in two or more regions; or LMN signs are found rostral to UMN signs and the diagnosis of Clinically Probable - Laboratory-supported ALS cannot be proven by evidence on clinical grounds in conjunction with electrodiagnostic, neurophysiologic, neuroimaging or clinical laboratory studies. Other diagnoses must have been excluded to accept a diagnosis of Clinically Possible ALS.

Table 1

	Brainstem	Cervical	Thoracic	Lumbosacral
Lower motor neuron signs weakness, atrophy, fasciculations	jaw, face, palate, tongue, larynx	neck, arm, hand, diaphragm	back, abdomen	back, abdomen, leg, foot
Upper motor neuron signs pathologic spread of reflexes, clonus, etc.	clonic jaw gag reflex exaggerated snout reflex pseudobulbar features forced yawning pathologic DTRs spastic tone	clonic DTRs Hoffman reflex pathologic DTRs spastic tone preserved reflex in weak wasted limb	loss of superficial abdominal reflexes pathologic DTRs spastic tone	clonic DTRs - extensor plantar response pathologic DTRs spastic tone preserved reflex in weak wasted limb