Trial No:	ZZ-3K3A-202
Title:	A Phase 2 Open Label Trial of 3K3A-APC in Amyotrophic Lateral Sclerosis.
Sponsor:	Macquarie University
Principal Investigator:	Dominic B Rowe PhD FRACP
Date of Protocol:	17 Mar, 2022
Version:	3.3.6
Commencement of Trial:	November, 2021

CONFIDENTIAL

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Investigator Agreement

3K3A-APC in Amyotrophic Lateral Sclerosis

I have carefully read this protocol including all appendices and agree that it contains all the necessary information for conducting the study safely.

I will conduct this study in strict accordance with this protocol and according to the current Good Clinical Practice (GCP) regulations and International Conference on Harmonization (ICH) guidelines, and local regulatory requirements. Any changes in procedure will only be made if necessary to eliminate immediate hazards and/or to protect the safety, rights or welfare of subjects.

I will provide copies of the protocol and all other information relating to this project, which were furnished to me, to all physicians and other study personnel responsible to me who participate in this study. I will discuss this information with them to assure that they are adequately informed regarding the conduct of the study.

I agree to keep records on all subject information (case report forms, informed consent statements and all other information collected during the study) in accordance with the current GCP, ICH, local, national and European regulations.

_____
Investigator Name

_____ _____
Investigator Signature Date

List of Abbreviations and Definitions

[^{18}F]FEMPA	N-{2-[2-[^{18}F]fluoroethoxy]-5-methoxybenzyl}-N-[2-(4-methoxyphenoxy)pyridine-3-yl]acetamide
Beta-HCG	Beta-human chorionic gonadotropin
CI	Confidence Interval
CRF	Case Report Form
CSF	Cerebrospinal fluid
CSOC	Clinical Study Oversight Committee
DNA	Deoxyribonucleic acid
DTI	Diffusion tensor imaging
ECAS	Edinburgh Cognitive and Behavioural ALS Screen
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HREC	Human Research Ethics Committee

List of Abbreviations and Definitions (continued)

ICH	International Conference on Harmonization
IUD	Intrauterine device
MBq	Megabecquerels
MRI	Magnetic Resonance Imaging
MGH	Massachusetts General Hospital
NOAC	Novel oral anticoagulants
PET	Positron Emission Tomography
PT	Preferred Term
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
ST	Symptomatic Therapy
TSPO	Translocator Protein
ULN	Upper Limit of Normal
UMN	Upper Motor Neuron
UMNS	Upper Motor Scale

3K3A-APC in ALS Protocol Synopsis

Protocol Number	ZZ-3K3A-202
Protocol Title	**A Phase 2 Open Label Trial of 3K3A-APC in Amyotrophic Lateral Sclerosis**
Sponsor	Macquarie University
Investigator	Professor Dominic Rowe
Study Centre	Macquarie University
Study Period	3 months
Study Objective and **Specific Aims**	The primary objective of this study is to determine the safety and potential effective dose of a novel therapy, 3K3A-APC in a small cohort (n=16) of patients with Amyotrophic Lateral Sclerosis (ALS). The specific aims to accomplish the primary objective are: a. To recruit patients with ALS according to established diagnostic criteria with Upper Motor Neuron features. b. To administer in a hospital environment two dose levels of a novel therapy, 3K3A-APC, to patients with ALS monitoring for safety. c. To investigate the biological effect of 3K3A-APC in the cohort employing a range of biometric, imaging and biological methods. d. To use the data from this pilot study to inform a larger study to assess the effectiveness of 3K3A-APC as a potential therapy to slow the progression of ALS.
Study Design	Cross sectional, single centre study to assess safety of 3K3A-APC in a small cohort of patients with clinically definite ALS, incorporating a range of imaging and biologic markers to determine the biological impact of the therapy.
Number of Subjects	16 Subjects Enrolled o Clinically Definite ALS according to Awaji Criteria o Established Upper and Lower Motor involvement

Main Eligibility Criteria	**Amyotrophic Lateral Sclerosis (ALS) Subjects:**
	
	Inclusion:
	
	• Patients must have clinically definite ALS (Awaji Criteria)
	
	• Male or female age 18 years and less than 75 years at time of ALS study.
	
	• Symptom onset less than 38 months before screening.
	  ○ *Participants who fail to meet this criterion may be considered at the Principal Investigator's discretion, provided the participant is clinically stable and without any safety concerns.*
	
	• Diagnosis of ALS less than 26 months before screening.
	  ○ *Participants who fail to meet this criterion may be considered at the Principal Investigator's discretion, provided the participant is clinically stable and without any safety concerns.*
	
	• Clinically definite Upper Motor Neuron signs
	
	Exclusion:
	
	• Current treatment with anticoagulants (e.g., warfarin, novel oral anticoagulants, heparin) that might preclude safe completion of the lumbar puncture.
	
	• Condition that precludes the safe performance of routine lumbar puncture, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia.
	
	• Use of investigational drugs or devices within 60 days prior to Baseline (dietary supplements taken outside of a clinical trial are not exclusionary, e.g., coenzyme Q10).
	
	• Prolonged prothrombin time or activated partial thromboplastin time >2xULN
	
	• Severe hypertension or hypotension
	
	• Glomerular filtration rate (GFR) <35 mL/min
	
	• Forced vital capacity (FVC) at screening of <50% of predicted.
	  ○ *Participants who fail to meet this criterion due to technical difficulties may be considered at the Principal Investigator's discretion.*
	
	• Prior exposure to any exogenous form of APC
	
	• Inability to lie flat for procedures (MRI, PET, LP).

	• Pregnant or lactating during the study period
Primary Outcome	The primary study outcomes are: To ensure the safety of patients with ALS administered a range of doses of 3K3A-APC according to a fixed dose regimen of five doses of 15mg or 30mg doses given 12 hours apart. This study also aims to determine whether a novel therapy, 3K3A-APC, is able to attenuate microglial activation in the motor cortex of patients with amyotrophic lateral sclerosis utilizing serial [^{18}F]FEMPA PET imaging (Day 2 and Day 9). In addition, the study design will include two (2) dose cohorts with eight patients in each cohort, with the initial cohort to receive 15mg and the subsequent cohort to receive 30mg, to determine the dose of 3K3A-APC that is shown to be most effective in reducing microglial activation. If microglial activation can be attenuated in ALS, then the progression of ALS might be slowed.

Secondary Outcomes	The secondary outcomes are:
	• Comparison between the changes in the mean of clinical, imaging and biomic outcomes in various subsets between the two dose cohorts.
	• The secondary outcome instruments to be employed are:
	  • MRI scan of the brain (Day 2 and Day 9), to determine whether the blood brain barrier integrity can be measured in ALS by Magnetic Resonance Imaging, and whether 3K3A-APC is able to repair it.
	  • Biomic measurements of serum, plasma, urine and CSF. This includes a novel method to determine whether monocyte activation in the peripheral blood can act as a surrogate marker of microglial activation state in ALS.
	  • These methods will determine whether 3K3A-APC therapy is able to attenuate the altered cytokine and metabolic profiles in ALS.

Safety Assessments	Incidence of adverse events, proportion of withdrawals due to adverse events, vital signs and clinical laboratory assessment changes from baseline. Clinical safety laboratory data (haematology, biochemistry, and urine chemistry) will be summarised at each protocol scheduled time point, by

	dose cohort, and overall. Observed values, change from baseline will be presented.
Statistical Methods	Descriptive analyses will be reported for this study. Continuous parameters, will be summarised as the number of observations, mean, median, standard deviation, minimum, maximum, and if appropriate two-sided 95% CI's. Categorical parameters will be summarised as frequencies, percentages, and exact Clopper-Pearson two-sided 95% CI's. Data will be summarised by dose cohort, and overall. Primary efficacy variables: Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) coding system to give a System Organ Class (SOC) and Preferred Term (PT) for each adverse event (AE). Treatment emergent AEs will be defined as AEs with an onset date on or after the date of administration of study drug. If the onset date is missing, the AE will be considered to be treatment emergent. Only treatment-emergent AEs will be summarized. All reported AEs will be listed. The number of AEs, and the number and percentage of patients reporting at least one AE will be summarized by PT nested within SOC for required AE types. AE data will be summarized by dose cohort, and overall. Microglial activation will be summarised at each time point for each dose cohort and overall as observed value, change from baseline, and % change from baseline. Microglial activation will be summarised with number of observations, mean, median, standard deviation, minimum, maximum, and two-sided 95% CI's. Secondary efficacy variables: The secondary efficacy variables of MRI scan of the brain, and biomic measurements of serum, plasma, urine and CSF will be summarized over time for each dose cohort, and overall as for the primary efficacy variables.
Data Access	Data will be password protected and securely stored at Macquarie University and with the contract data management team. All personally identifiable information will be removed before it is shared outside the study.

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Schedule of Activities – ALS Subjects

Visit Number	**SC**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**
Day of the Week		**M**	**T**	**W**	**T**	**F**	**S**	**S**	**M**	**T**	**W**	**M**
Visit Description (Day)	**-30**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**15**
Written Informed Consent	X											
Inclusion/Exclusion Criteria	X	X										
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X							X			X
Neurological Examination	X	X							X			X
ECAS	X											
FVC	X											
ECG	X	X	X	X	X	X			X	X	X	X
Pregnancy Test (Urine)	X	X							X			
Blood Sample for TSPO genotype	X											
Clinical Laboratory Assessments	X[a]	X	X	X[a]	X[a]	X[a]	X	X	X	X	X[a]	X[a]
Research blood and urine samples	X	X	X	X	X	X			X	X	X	X
Lumbar Puncture for CSF examination				X							X	

Visit Number	**SC**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**
Day of the Week		**M**	**T**	**W**	**T**	**F**	**S**	**S**	**M**	**T**	**W**	**M**
Visit Description (Day)	**-30**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**15**
MRI (ALS Protocol)			X							X		
PET imaging ([^{18}F]FEMPA)			X							X		
Administration of 3K3A-APC – 5 doses (every 12 hours)				X	X	X						

a – Urine collected for urinalysis

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1. Introduction and Rationale for this Study

Multiple mechanisms are suggested to be involved in the cause of sporadic ALS, with evidence for many pathogenic processes, none of which clearly lead to significant therapies. These include excitotoxicity, oxidative stress, impaired cellular defence mechanisms and immune-mediated inflammation, to name just a few. There is considerable evidence that inflammation is central in the pathogenesis of ALS. Microglia are critical in this inflammatory response, both as detectors of motor neuronal injury and in the effector response that ultimately produces motor neurone death and progression of disease. The earliest change that occurs in the pathology of ALS is activation of microglia, both in post-mortem human ALS tissue and in animal models of ALS. Activated microglia and astrocytes are found in close proximity to dying motor neurons. Their activation status and proliferation seemingly increases with disease progression.

Inflammatory microglia and monocytes have been considered as a therapeutic target in ALS, but to date only a few trials exist where attenuation of microglial activation is the principal mechanism of action (1).

It is now possible to measure *in vivo* activated microglia in the CNS utilizing a PET imaging technique targeting the microglial 18kD translocator protein, TSPO. In a small trial of 10 patients, Zurcher et al were able to show that [^{11}C]-PBR28 positron emission tomography revealed increased binding in the motor cortices and corticospinal tracts in patients with ALS compared to healthy controls (2). This technique may therefore be utilized to measure end organ effectiveness of a therapeutic intervention to downregulate microglial activation, and has been replicated in further studies, including therapeutic studies in other diseases (3). We now have access to an ^{18}F ligand for TSPO termed FEMPA (Piramal) at Macquarie University in collaboration with Cyclotek and Piramal (4).

APC is an endogenous serine protease with systemic anticoagulant, anti-inflammatory, and anti-apoptotic activities. 3K3A-APC is a 405-residue protein expressed via recombinant technology in Chinese hamster ovary (CHO) cells. Its amino acid sequence differs from that of the wild-type human Activated Protein C (APC) and of the product drotrecogin alfa (activated) (Xigris®) in that 3 sequential lysine residues have been replaced with 3 sequential amino-acid substitutions (all lysine to alanine); the amino acid substitutions are K191A-K192A-K193A. This change retains the cytoprotective effects of native (wild-type) APC while significantly reducing its anticoagulant effects. 3K3A-APC is an APC variant that has been genetically engineered to maximize neuro- and cytoprotective activity and minimize anticoagulant activity. 3K3A-APC is currently in development for the treatment of moderate to severe acute ischemic stroke (ZZ Biotech – see investigational brochure). A Phase 1 trial of 3K3A-APC was completed in healthy volunteers (NCT01660230), with demonstrated safety. Intravenous administration of 3K3A-APC in multiple dose levels did not result in any serious adverse events, severe adverse events or withdrawal from study due to an adverse event (5). A Phase 2 trial of 3K3A-APC in Ischemic Stroke

(NCT02222714) has also finished (6). The doses of 3K3A-APC being evaluated in the study were 120, 240, 360 and 540 µg/kg. These doses were based on the doses and administration that were tested in the Phase 1 clinical study in normal human volunteers during which single- and multiple-dose (q12 hours for 5 doses) infusions were well tolerated at doses up to 540 µg/kg. Further study has demonstrated no relationship between clearance and body weight, so further ongoing trials with 3K3A-APC now utilize fixed doses to achieve the same blood levels of the investigational product.

3K3A-APC's cytoprotective activities are mediated by proteolytic activation of protease activated receptor 1. In addition, it has been shown that 3K3A-APC has powerful anti-inflammatory action, with reduction of microglial numbers and activation state. In 2009, Zhong et al demonstrated in mutant superoxide dismutase-1 (SOD1) mice that administration of 3K3A-APC after disease onset slows disease progression and extends survival (7). Furthermore, Winkler et al were able to show that blood brain barrier (BBB) breakdown contributes to early motor-neuron degeneration in ALS mice and that restoring BBB integrity via 3K3A-APC during an early disease phase retards the disease process (8).

We propose to use two different doses regimens of 3K3A-APC (15mg and 30mg), similar to doses demonstrated to be safe in stroke patients, in two cohorts of patients with Amyotrophic Lateral Sclerosis. This study will determine safety and tolerability in ALS patients. In addition cerebral [^{18}F]FEMPA PET imaging will determine whether microglial activation can be modulated from prior to the infusion (Day 2) to after completion of the infusion (Day 9). An MRI method recently developed by the team at Macquarie University will also be used to assess diffusion kurtosis and integrity of the blood brain barrier (9). Other biomarkers of microglial/monocyte activation will be assayed including kynurenine metabolites in plasma, serum and urine, monocyte activation state in peripheral blood via flow cytometry and proteomics including cytokine and chemokine assays, neurofilaments assays and measurement of soluble CD14.

If microglial activation can be attenuated in ALS, then the progression of ALS might be slowed. While this is an acute dosing study over a short period, the information derived from this study will inform chronic long-term dosing trials for patients with ALS.

2. Study Design

ZZ-3K3A-APC-202 is a phase II, single centre, open label, uncontrolled cohort trial of 15mg (initial cohort) and 30mg of 3K3A-APC given twice daily intravenously for a maximum of 5 doses to patients with ALS. Each patient will be admitted to hospital for dosing. For each patient, the trial will run for two weeks, including a ten-day hospital stay for 3K3A-APC IV administration and study evaluations. The study has an estimated completion time of three months. A maximum of 8 patients will participate in each cohort.

3. Study Objectives

3.1 Primary Objective

The primary study outcome is the safety of patients with clinically definite ALS administered given up to 5 doses of either 15mg or 30mg of 3K3A-APC 12 hourly. Safety will be evaluated by clinical laboratory testing, physical examination and the collection of adverse events.

In addition, this study aims to determine which dose of 3K3A-APC treatment is able to attenuate microglial activation in the motor cortex of patients with amyotrophic lateral sclerosis, utilizing [^{18}F]FEMPA PET imaging prior to, and after treatment. In addition, the study will determine the dose of 3K3A-APC that is most effective in reducing microglial activation.

3.2 Secondary Objectives

The secondary outcomes are the comparison between the changes in the mean of clinical, imaging and biomic outcomes in various subsets between the two groups. The secondary outcome instruments are:

MRI scan of the brain (Day 2 and Day 9), to determine whether the blood brain barrier integrity can be measured in ALS by Magnetic Resonance Imaging, and whether 3K3A-APC is able to repair it. In addition novel methods of measuring diffusion kurtosis, a marker of neuronal injury will be used.

Extensive biomic measurements of serum, plasma, urine and CSF will be performed. These will include a novel method to determine whether monocyte activation in the peripheral blood can act as a surrogate marker of microglial activation state in ALS. In addition multiplex cytokine and chemokine assays will determine the biological impact of the therapy. Neurofilament, soluble CD14 and kynurenine (and other) measurements will be used to look at acute changes as a result of 3K3A-APC. These methods will determine whether 3K3A-APC therapy is able to attenuate the altered cytokine and metabolic profiles in ALS.

It is highly unlikely that such an acute dosing regimen will identify neurological changes in the subjects, but accurate clinical and biophysical measurements will be performed to detect any such change should they occur.

4. Study Outcome

The mean rates of change and the variability around the mean of clinical, imaging and biomic outcomes in the two ALS patient cohorts will be determined over the study period. The results will inform potential future studies of the therapeutic potential of 3K3A-APC in ALS patients, and guide dosing for chronic studies.

5. Participants

5.1 Study setting and recruitment

Participants will be recruited from the ALS clinic at Macquarie University. Participants will be approached regarding the trial where possible, in routine follow up clinics. Alternatively potential participants may be approached in writing or by email by the investigators to invite them for screening.

Participants will be hospitalised at Macquarie University Hospital. PET scans and MRI scans, and lumbar punctures will be conducted at Macquarie Medical Imaging.

5.2 Selection of Study Population

5.2.1 Inclusion Criteria

- Age 18-75 years at the time of the screening visit
- Able to provide informed consent in accordance with Good Clinical Practice (GCP), International Conference on Harmonization (ICH), and local regulations
- Willing and able to comply with scheduled visits, required study procedures and laboratory tests
- Symptom onset less than 38 months before screening
  - *Participants who fail to meet this criterion may be considered at the Principal Investigator's discretion, provided the participant is clinically stable and without any safety concerns.*
- Diagnosis of ALS less than 26 months before screening
  - *Participants who fail to meet this criterion may be considered at the Principal Investigator's discretion, provided the participant is clinically stable and without any safety concerns.*
- ALS diagnosed as definite according to the Awaji Criteria.
- Both sporadic and monogenic forms of ALS are to be included.
- Must be on a stable dose of riluzole for at least 30 days prior to the screening visit.

- Clinically definable Upper Motor Neurone signs such as increased tone, clonus, hyper-reflexia and/or extensor plantar responses
- Women may not be pregnant, lactating or planning pregnancy during the course of the study.
    - Includes a negative urine pregnancy test on day of the PET scan prior to injection ([^{18}F]FEMPA).

Women participants and female partners of participating men must be of non-childbearing potential **or** be using a highly effective method of birth control 14 days prior to until at least 24 hours after injection of [^{18}F]FEMPA.

- Non-child bearing potential is defined as a female that must be either postmenopausal (no menses for at least 12 months prior to Screening) or a female or male that is surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy, sterilization).
- Highly effective method of birth control is defined as practicing at least one of the following: A birth control method that results in a less than 1% per year failure rate when used consistently and correctly, such as oral contraceptives for at least 3 months prior to injection, an intrauterine device (IUD) for at least 2 months prior to injection, or barrier methods, e.g., diaphragm or combination condom and spermicide. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) is not acceptable.

5.2.2 Exclusion Criteria

- Motor Neurone Disease syndromes that do not have clinically detectable Upper Motor Neurone signs (e.g., flail arm or flail leg onset of ALS)
- A clinical diagnosis of dementia as determined by the Investigator.
- Current treatment with anticoagulants (e.g., warfarin, novel oral anticoagulants, heparin) that might preclude safe completion of the lumbar puncture.
- Condition that precludes the safe performance of routine lumbar puncture, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia.
- Use of investigational drugs or devices within 60 days prior to baseline (dietary supplements taken outside of a clinical trial are not exclusionary, e.g., coenzyme Q10).

- Prolonged prothrombin time or activated partial thromboplastin time >2xULN
- Severe hypertension or hypotension
- Glomerular filtration rate (GFR) <35 mL/min
- Prior exposure to any exogenous form of APC
- FVC at screening of <50% of predicted
  - *Participants who fail to meet this criterion due to technical difficulties may be considered at the Principal Investigator's discretion.*
- Inability to lie flat for investigational procedures (MRI, PET, Lumbar Puncture)
- Previously obtained MRI scan with evidence of clinically significant neurological disorder (in the opinion of the Investigator).
- Presence of any of the following clinical conditions at the time of screening:
  - Drug or alcohol abuse, unstable medical disease (such as unstable angina or chronic obstructive pulmonary disease), active infectious disease (such as Hepatitis B or C or tuberculosis), current malignancy, unstable psychiatric illness (based on a prior psychiatric diagnosis that is unstable as determined by the subject's treating Psychiatrist) defined as psychosis or untreated major depression within 90 days of the screening visit, or any other condition that, in the opinion of the Investigator, might interfere with study conduct or interpretation of the study results.

6. Investigational Plan

6.1 Participant Identification Numbers

A participant ID Number will be assigned in sequential order to all patients who consent to screening. This unique 2-digit participant number for subjects will be used to identify the participant on all study forms and lab specimens.

6.2 Schedule of Activities

Refer to the protocol synopsis Schedule of Activities that summarizes the assessments to be conducted

6.2.1 Screening Visit

All subjects will undergo a screening evaluation prior to the Baseline visit. This evaluation will include the following activities and will take about 2 hours to complete:

- An explanation of the purpose, procedures, potential risks and benefits of this study and informed consent will be obtained
- Demographics
- Review of the subject's medical and family history
- Review of concomitant medications
- Vital signs (blood pressure, heart rate and temperature)
- General physical examination
- Neurological examination (ALSFRS-R, MGH Upper Motor Neuron scale assessment (MGH UMN))
- Edinburgh Cognitive and Behavioural ALS Screen (ECAS)
- Collect blood sample for DNA for TSPO genotype
- Blood and urine collection for clinical laboratory assessments
- Blood and urine collection for research samples
- Urine pregnancy test for women of childbearing potential.
- Electrocardiogram (ECG)
- Forced Vital Capacity (FVC)
- A review of the inclusion/exclusion criteria to confirm that the subject is eligible to continue to the Baseline visit

6.2.2 Baseline Assessments (Day 1, 2 and 3):

The activities for the Baseline Assessments will be completed within 30 days of completing the Screening visit. Screening and Day 1 can occur on the same day.

Baseline assessments will include the following activities and will take Day 1-3 to complete, as listed in the schedule of activities. These assessments and subsequent activities will occur as an inpatient of Macquarie University Hospital. All assessments listed below must be completed prior to enrollment of the subject into the treatment phase of the study.

- Review of continuing ability to consent
- Vital signs (blood pressure, heart rate and temperature), height and weight
- Physical examination
- ECG

- Blood collection for clinical laboratory assessments (daily)
- Urinalysis (day 3)
- Blood and urine collection for research samples (daily)
- Urine pregnancy test (Day 1)
- Neurological exam (incl. ALSFRS-R and UMN Index)
- Brain MRI (Day 2)
- Brain PET Imaging (Day 2)
- Lumbar puncture for collection of CSF (Day 3)
- Review of concomitant medications
- Review of current medical conditions
- Review of adverse events related to lumbar puncture
- Repeat review of the inclusion/exclusion criteria

Once all Visit 1 activities have been completed and the Investigator determines that all eligibility criteria have been met, the subject may be enrolled into the study. Once enrolled, the subject will be enrolled in one of two dose levels of 3K3A-APC (15mg or 30mg).

6.2.3 Inpatient Daily Assessments (Visit 4-10, Days 4-10)

Administration of 3K3A-APC will occur as an inpatient of Macquarie University Hospital at 12 hourly intervals commencing Day 3 and continuing to Day 5.

Subjects will be assessed daily while inpatients in Macquarie University Hospital. The assessments are outlined in the schedule above and will include:

- Vital signs (Daily)
- ECG (Daily, excluding day 6 and 7)
- Clinical laboratory assessments (EUC, LFT, FBC, APTT, PT)
- Urinalysis (Day 4, 5,10)
- Research blood and urine samples (Daily, excluding day 6 and 7)
- Urine pregnancy test (Day 8)
- Physical examination (Day 8)
- Neurological examination (ALSFRS-R, MGH UMN scale) (Day 8)
- Repeat MRI Brain (Day 9)
- Repeat PET Imaging (Day 9)

- Repeat Lumbar puncture (Day 10)
- Assessment of adverse events (Daily)

Following completion of Day 10 assessments, the subject will be discharged home for follow up as an outpatient for the end of study visit (Visit 11).

6.2.4 End of Study Assessment (Visit 11 Day 15)

The end of study visit will be completed as an outpatient. End of study assessments will include:

- Vital signs
- ECG
- Physical examination
- Neurological examination (ALSFRS-R, MGH UMN Scale)
- Blood and urine collection for clinical laboratory assessments
- Blood and urine collection for research samples
- Assessment of adverse event

6.2.5 Early termination visit

All patients who discontinue early from the study should return to the clinic to complete the procedures for Visit 11. Study personnel should make every effort to conduct all protocol-specified procedures to complete the study.

7. Study Assessments

7.1 Clinical Assessments

7.1.1 Vital Signs

Blood pressure, heart rate and temperature will be measured at every visit via standard methods. Height and weight will be recorded at baseline.

7.1.2 General Physical Examination

At screening and baseline (Day 1), Visit 8 and Visit 11, a general physical examination will be recorded by the investigator including cardiac, respiratory, abdominal examination.

7.1.3 Neurological Examination

Standardised neurological examination will be performed by the principal investigator at screening, Visit 1, Visit 8 and Visit 11. This will include standardised assessments of UMN features such as tone, reflexes and primitive reflexes (plantar response). Assessment of motor function will be determined in standardised fashion (MRC grade, pinch grip and grip strength). ALSFRS-R and UMN Scale will be assessed and calculated.

7.1.3 Electrocardiograph

A standard 12 lead ECG will be recorded at screening, baseline and each visit of the study (excluding day 6 and 7) via standard methods.

7.1.4 Forced Vital Capacity

Forced vital capacity in the standing or seated position will be obtained via standard methods at screening.

7.1.5 Clinical Laboratory Tests

Routine clinical laboratory tests indicated in the table below will be performed at screening and follow up visits according to the visit schedule. A central laboratory (Sonic) will be implemented in order to guarantee identical analysis methods, consistent normal ranges and thus common interpretation of laboratory changes. If not stated otherwise, venous whole blood will be collected in blood collection tubes (vacutainers).

The coagulation panel (PT/APTT) will be reviewed by the Investigator prior to lumbar puncture.

No more than 40 mL will be drawn at any visit, including both clinical and research blood samples (see 7.2.4 below).

CLINICAL LABORATORY TESTS	
METABOLIC PANEL	**BLOOD COUNT**
Sodium (Na) Potassium (K) Chloride (Cl) Bicarbonate (HCO3) Urea Glucose Calcium (Ca) Creatinine (Cr) Bilirubin Total Albumin Total Protein Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline Phosphatase (ALP) Creatinephosphokinase (CPK) Iron studies (Fe, Ferritin) Prothrombin time (PT) Activated Partial Thromboplastin Time (APTT)	White Blood Cell Count (WBC) Red Blood Cell Count (RBC) Hemoglobin (Hb) Hematocrit (HCT) Platelet Count (PLT)

As part of the clinical laboratory tests, urine will be collected for urinalysis at screening, day 3-5., day 10 and day 15.

A urine pregnancy test will be conducted at screening and prior to [^{18}F]FEMPA PET scan on Visit 1 and Visit 8.

All samples for laboratory analysis must be collected, prepared, labelled, and shipped according to the laboratory's requirements.

7.1.6 Adverse Events

During each visit participants will be asked about adverse events. AEs will be recorded on an ongoing adverse event log.

7.1.7 Concomitant Medications

All concomitant medications during hospitalization will be recorded on a log.

7.2 Other Assessments

7.2.1 TSPO Genotyping

A sample of venous blood will be collected at screening for DNA extraction to be used for TSPO genotyping to determine whether subjects have high affinity, mixed affinity or low affinity binding for the TSPO ligand according to established methods (10).

7.2.2 Microglial PET Imaging

Subjects will undergo [^{18}F] FEMPA PET imaging to assess the activation state of microglia in the brain. On Day 2 and Day 9 subjects will receive approximately 200 MBq of [^{18}F] FEMPA with dynamic brain scanning from time=0 to 50 minutes according to previously established protocols. Scanning time will be 50 minutes in total.

7.2.3 Brain MRI (ALS protocol)

Subjects will undergo a structural MRI brain scan on Day 2 and on Day 9 according to established protocols (9). At the discretion of the investigator and imaging staff, subjects who have presence of pacemakers, aneurysm clips, artificial heart valves, cochlear implants, metal fragments or foreign objects in the eyes, skin or body or any other known contra-indication to MRI may be advised not to complete a baseline (or follow-up) MRI scan, but these subjects may still participate in the study. MRI is being conducted to assess the structure of the brain, for co-registration with PET images as well as assessing the integrity of the blood brain barrier.

7.2.4 Biomic Blood and Urine samples

Whole blood (8 mL), serum (about 10 mL) and plasma (about 10 mL) will be collected to conduct proteomic, metabolomic and other analyses. Urine (about 10 mL) will be collected to conduct analyte analyses. Where possible the research blood samples will be collected in a fasted state (i.e., minimum of 8 hours since last meal/food intake) to ensure the quality of samples for future analyses. All research samples will be stored indefinitely for research purposes.

7.2.5 Lumbar Puncture for CSF Examination

The lumbar puncture (LP) will be performed under image intensifier by a qualified radiologist appointed by the investigator. A lumbar puncture for the collection of 10 mL of CSF will be conducted for all subjects at Visit 3 and Visit 10 unless there is evidence of clinically significant coagulopathy or thrombocytopenia that would interfere with the safe conduct of the procedure. The first 2 mL of CSF will be processed at the local laboratory facility to conduct standard analyses on cell count, protein and glucose levels. Subjects will be closely monitored during the procedure and following the procedure. The CSF samples will be stored indefinitely for research purposes for analytes relevant to inflammation and monocyte activation.

8. Study Medications

8.1 Study medication dose, packaging and labelling

3K3A-APC is supplied frozen in vials of 5mg at a concentration of 1.0mg/mL. Upon thawing, the sterile solution is clear and requires dilution in 0.9% sodium chloride for intravenous infusion. 3K3A-APC will be prepared for infusion by clinical trials pharmacist using aseptic technique. For the first treatment cohort, 3 vials of 3K3A-APC will be diluted to 100mL. For the second cohort, 6 vials of 3K3A-APC will be diluted to 100mL. See pharmacy manual for more information regarding study medication handling.

Infusion bags will be labelled by the clinical trials pharmacist with study name (3K3A-APC in ALS) and protocol number (ZZ-3K3A-202), patient name and study number, and medication name (3K3A-APC) and concentration.

8.2 Study medication administration

The study medication must be infused within 8 hours of preparation.

The 100mL of study medication will be administered by IV infusion over 15 minutes (by pump set to 400mL/hr). Five doses of study medication will be administered at 12 hourly intervals ± 1 hour starting on day 3 of hospitalization and finishing on day 5 of hospitalisation. Study drug should be flushed from infusion line with 0.9% sodium chloride.

If a hypersensitivity reaction develops, infusion is stopped immediately and no further doses of study medication will be administered.

8.3 Prohibited Concomitant Medications

Anticoagulant medications are prohibited during the treatment period, and for 7 days prior and 7 days post study drug administration. Anticoagulant medications include heparins, low molecular weight heparins, novel oral anticoagulants (e.g. dabigatran, rivaroxaban and apixaban), warfarin.

Medications that might interfere with monocyte activation such as systemic corticosteroids or immune suppressants are prohibited from screening visit until follow up at day 15.

It is preferred that subjects do not participate in clinical trials of other investigational interventions during the entire study.

All concomitant medications reported at the time of the screening visit and for the duration of the subject's participation should be recorded on the Concomitant Medication Log.

9. Subject Withdrawals

Subjects will be advised in the written informed consent forms that they have the right to withdraw from the study at any time without prejudice, and may be withdrawn at the investigator's or sponsor's discretion at any time. A subject

should be withdrawn from the study if the investigator considers it to be medically necessary, or if the subject withdraws consent. All reasons for subject withdrawals from the study will be recorded in the source documentation and appropriate eCRF.

10. Safety/Adverse Events

Site investigators and coordinators will be instructed to assess for adverse events at in-person study visits.

10.1 Adverse Event Definitions

Adverse Events (AE)

An AE is any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational product.

Pre-existing conditions (i.e., undesirable experiences, signs or symptoms that begin prior to the Screening Visit) will be recorded on the medical history CRF page. These conditions will not be reported as an AE unless they worsen in intensity or frequency after the Screening Visit.

Treatment-emergent AEs are undesirable experiences, signs, or symptoms that begin or worsen in intensity or frequency at the time of or after the administration of study drug.

Serious Adverse Event (SAE)

An SAE is an AE that is fatal or life-threatening, or results in prolongation of hospitalization, persistent or significant disability/incapacity. A life-threatening AE is an AE that, in the view of the investigator, places the subject at immediate risk of death from the event, as it occurred. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Unexpected Adverse Event

For FDA reporting purposes, an unexpected AE is an AE not previously reported or an AE that occurs with specificity, severity or frequency that is not consistent with the current investigator's brochure.

10.2 Relationship to Investigational Product

The assessment of the relationship of an AE to the administration of the study drug is a clinical decision based on all available information at the time the event is being documented. The following definitions of the relationship between the study drug and the AE (including SAEs) should be considered:

- Unrelated - No possible relationship

The temporal relationship between drug exposure and the adverse event onset/course is unreasonable or incompatible, or a causal relationship to study drug is implausible.

- Unlikely - Not reasonably related, although a causal relationship cannot be ruled out

While the temporal relationship between drug exposure and the adverse event onset/course does not preclude causality, there is a clear alternate cause that is more likely to have caused the adverse event than the study drug.

- Possible - Causal relationship is uncertain

The temporal relationship between drug exposure and the adverse event onset/course is reasonable or unknown, de-challenge or re-challenge information is either unknown or equivocal, and while other potential causes may not exist, a causal relationship to the study drug does not appear probable.

- Probable - High degree of certainty for causal relationship

The temporal relationship between drug exposure and the adverse event onset/course is reasonable. There is a clinically compatible response to de-challenge (re-challenge is not required), and other causes have been eliminated or are unlikely.

- Definite - Causal relationship is certain

The temporal relationship between drug exposure and the adverse event onset/course is reasonable, there is a clinically compatible response to de-challenge, other causes have been eliminated, and the event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.

10.3 Intensity/Severity of an Adverse Event

In addition to assessing the relationship of the administration of the investigational product to AEs, an assessment is required of the intensity (severity) of the event. The following classifications should be used:

- *Mild:*
  A mild AE is an AE, usually transient in nature and generally not interfering with normal activities.

- *Moderate*:
  A moderate AE is an AE that is sufficiently discomforting to interfere with normal activities.

- *Severe:*
  A severe AE is an AE that incapacitates the subject and prevents normal activities. Note that a severe event is not necessarily a serious event. Nor must a serious event necessarily be severe.

10.4 Recording of Adverse Events

Adverse events including clinical significant biological sample test abnormalities,, whether observed by the investigator, elicited from or volunteered by the subject, should be recorded on the Adverse Event Log. This will include a brief description of the experience, the date of onset, the date of resolution, the severity, and seriousness and whether the event was related to participation in the research study.

10.5 Responsibilities for Reporting Serious Adverse Experiences

- The Investigator should notify the sponsor within 24 hours of his/her becoming aware of the occurrence of a serious adverse experience or suspected unexpected serious adverse reaction (SUSAR).
- The following information should be supplied if available at the time of the email or telephone call: subject number, subject age and gender, date of onset of event, event description, whether event required treatment, death and autopsy report, an identification of which criteria for a serious experience have been met, the Investigator's current opinion of the relationship between the event and study participation.
- The Investigator will comply with Macquarie University HREC regulations regarding the reporting of adverse experiences.

11. Referrals for Unexpected Results of Study Participation

If a research assessment, lab or MRI result reveals a clinically significant abnormality (e.g., renal impairment on metabolic profile) the subject should be informed of this result and the Investigator should provide the subject with the appropriate referral as necessary.

12. Potential Risks

12.1 Blood Sampling

Risks associated with venous blood draw include pain and bruising at the site where the blood is taken. Sometimes people can feel lightheaded or even faint after having blood drawn.

12.2 Lumbar Puncture

The most common risks of a lumbar puncture are pain at the site and a temporary headache usually due to a small amount of CSF leakage around the needle insertion site. Lying down for a few hours after the test can make a headache less likely to occur. There is a slight risk of infection because the needle breaks the skin's surface, providing a possible portal of entry for bacteria. A temporary numbness to the legs or lower back pain may be experienced. There is a small risk of bleeding in the spinal canal. Subjects will have blood drawn at Screening to test for coagulopathies.

12.3 MRI – ALS Protocol

Subjects should notify the study doctor if they suffer from claustrophobia because they may become anxious while in the magnetic resonance scanner. There may be loud noises such as knocking or hammering that occur while the MRI is being conducted. Subjects should also inform the study doctor if they have a pacemaker or metal implants (screws, plates or clips) because this may preclude MR evaluation. The imaging will take 60 minutes.

12.4. PET Imaging

Specific potential risks for PET imaging are as follows:

1) radiation exposure from [^{18}F]FEMPA
2) (see companion protocol),
3) having an intravenous injection.

12.5 Unknown Risks

In addition to the known risks listed above, the imaging procedures in this study may cause unknown risks to the participant, or a developing embryo or fetus or possible risks to the future offspring of male participants. Female subjects or a female partner of a male subject who report a pregnancy within 30 days of [^{18}F]FEMPA injection will be asked to have a urine pregnancy test.

13. Regulatory / Ethics

13.1. Compliance Statement

This study will be conducted in accordance with the Good Clinical Practice (GCP) and the International Conference on Harmonization (ICH) guidelines and any applicable national and local regulations.

All procedures not described in this protocol will be performed according to the study Operation Manuals unless otherwise stated. Laboratory tests/evaluations described in this protocol will be conducted in accordance with quality laboratory standards as described in the central laboratory manual unless otherwise stated.

13.2. Informed Consent

In accordance with relevant regulations, an informed consent agreement explaining the procedures and requirements of the study, together with any potential hazards/risks must be read by and explained to each subject. Each subject will sign such an informed consent form. The subject must be assured of the freedom to withdraw from participation in the study at any time.

It is the Investigator's responsibility to make sure that the subject understands what she/he is agreeing to and that written informed consent is obtained before

the subject is involved in any protocol-defined procedures including screening procedures. It is also the Investigator's responsibility to retain the original signed consent form and provide each subject with a copy of the signed consent form.

The Project Management Team must be given an opportunity to review the consent forms prior to site Human Research Ethics Committee (HREC) submission and before it is used in the study.

13.2 Human Research Ethics Committee Review

All necessary information will be supplied by the Investigator including the protocol and consent forms to the HREC for review and approval. The Investigator agrees to provide the HREC all appropriate material. The trial study will not begin until the Investigator has obtained appropriate HREC approval. A copy of the approval letter and approved consent form must be submitted to the CRO.

The Investigator will request from the HREC a composition of the members reviewing the protocol and informed consents. Appropriate reports on the progress of this study by the Investigator will be made to the HREC and the CRO in accordance with institutional and government regulations. The CRO will notify the site when the HREC may be notified of study completion. It is the Investigator's responsibility to notify the HREC when the study ends. This includes study discontinuation, whether it is permanent or temporary. A copy of the site HREC acknowledgement of study completion must be submitted to the Project Management Team.

13.3. Protocol Amendments

Changes to the protocol should only be made via an approved protocol amendment. Protocol amendments must be approved by the study's Steering Committee and the HREC prior to implementation, except when necessary to eliminate hazards and/or to protect the safety, rights or welfare of subjects.

13.4 Subject Confidentiality

The site Investigator must assure that the confidentiality of subjects, including their personal identity and personal medical information, will be maintained at all times. Subjects will be identified by consecutive ID numbers issued by the data management team on case report forms and other study materials submitted to data management, the pathology laboratory, and bio-repository.

After a subject signs an informed consent form, it is required that the site Investigator permit regulatory agency personnel to review the signed informed consent(s) and that portion of the subject's medical record that is directly related to the study. This shall include all study relevant documentation including subject medical history to verify eligibility, laboratory test result reports, admission/discharge summaries for hospital admissions occurring while the subject is in the study, and autopsy reports for deaths occurring during the study (when available).

13.5 COVID-19 Contingency Plan

The COVID-19 pandemic and the restrictions imposed by the NSW government present an unprecedented challenge to clinical trials. However, compliance and adherence to these regulations and the recommendations of Macquarie University is a priority in order to maintain the safety of staff and trial participants.

The following protocol modifications will be applied as deemed appropriate by the Principal Investigator in accordance with COVID-19 regulations:

- The exclusion criteria of *forced vital capacity (FVC) at screening of <50% of predicted* will not be assessed as part of eligibility for trial participation.
- The inclusion criteria of:
  - *symptom onset less than 36 months before screening*
  - *diagnosis of ALS less than 24 months before screening*

  will be re-assessed by the Principal Investigator in the event that a trial participant's eligibility is affected by delays to their randomization date.

14. Documentation

14.1 Study File and Source notes

The Investigator shall maintain and retain site documentation consistent with the requirements of the TGA annotated ICH-GCP. Source notes will include all printouts/reports of tests/procedures, as specified in the protocol, for each subject. This documentation, together with the subject's hospital/medical records, and the participant's original signed consent form is the subject's source information for the study.

15. Statistical Analysis

15.1 Demographic and Baseline Characteristics

Descriptive analyses will be reported for this study. Continuous parameters, will be summarised as the number of observations, mean, median, standard deviation, minimum, maximum, and if appropriate two-sided 95% CI's. Categorical parameters will be summarised as frequencies, percentages, and exact Clopper-Pearson two-sided 95% CI's. Data will be summarised by dose cohort, and overall.

15.2 Primary efficacy variables

Adverse events will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) coding system to give a System Organ Class (SOC) and Preferred Term (PT) for each adverse event (AE).

Treatment emergent AEs will be defined as AEs with an onset date on or after the date of administration of study drug. If the onset date is missing, the AE will be considered to be treatment emergent. Only treatment-emergent AEs will be summarized. All reported AEs will be listed. The number of AEs, and the number and percentage of patients reporting at least one AE will be summarized by PT nested within SOC for required AE types. AE data will be summarized by dose cohort, and overall.

Microglial activation as measured by [^{18}F] FEMPA will be summarised at each time point for each dose cohort and overall as observed value, change from baseline, and % change from baseline. Microglial activation will be summarised with number of observations, mean, median, standard deviation, minimum, maximum, and two-sided 95% CI's.

15.3 Secondary efficacy variables:

The secondary efficacy variables of MRI scan of the brain, and biomic measurements of serum, plasma, urine and CSF will be summarized over time for each dose cohort, and overall as for the primary efficacy variables.

15.4 Clinical Safety Laboratory data

Clinical safety laboratory data (haematology, biochemistry, and urine chemistry) will be summarised at each protocol scheduled time point, by dose cohort, and overall. Actual values and actual changes from baseline will be presented.

Urinalysis results evaluation (normal, abnormal not clinically significant or abnormal clinically significant) will be summarised at each protocol scheduled time point, by dose cohort with frequency tabulations.

15.5 Vital Signs

Vital sign measurements will include height, weight, body mass index (BMI), body temperature, respiratory rate, heart rate and systolic and diastolic blood pressure. Vital signs will be collected at the times stipulated in the Protocol Schedule of Assessments.

Vital sign results will be summarised at each protocol scheduled time point, by dose cohort and overall. Actual values and actual changes from baseline will be presented.

15.6 Physical and Neurological Examinations

A physical examination and neurological examinations will be performed at times stipulated in the Protocol Schedule of Assessments. Physical examination and neurological findings will be listed by Visit and Participant. Clinically significant changes will be captured as adverse events.

16. Data Management

An Internet accessible Electronic Data Capture (EDC) system for data management will be utilized for this study, designed by the data management team. This system will be protected by 128-bit server certificates and will utilize authenticated, password-protected accounts for each investigator. The EDC system will be designed to ensure timeliness and accuracy of data as well as the prompt reporting of data from the study. The system will be compliant with relevant FDA regulatory requirements per 21 CFR Part 11 and will be stored on an Australian based server.

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Data review, coding and query processing will be done through interaction with the data management team, site personnel and the Study Monitor. Queries will be generated in real-time as data are entered. Once the data are submitted to the EDC system, they are immediately stored in the central study database located at McLeod Consulting Group and will be accessible for review by data management staff. Any changes to the data will be fully captured in an electronic audit trail. As data recorded by sites in eCRFs are received, narrative text of adverse experiences and concomitant medications will be periodically coded using established coding mechanisms.

The cycle of electronic data entry, review, query identification/resolution, and correction occurs over the course of the study period until all subjects have completed the study.

Data will be securely maintained by the data management team. Once the data management team, in conjunction with the principal investigator agree that all queries have been adequately resolved and the database has been deemed "clean." The database will be officially signed off and deemed locked. All permissions to make changes (append, delete, modify or update) the database are removed at this time.

All data obtained during the conduct of the study, will be stored indefinitely for research purposes. Research data will be made available to researchers to conduct analyses if requested and if required for publication in peer-reviewed journals.

17. Study Monitoring

In accordance with TGA annotated ICH Guidelines for Good Clinical Practice. The study will be monitored by an independent Clinical Trial Monitor reporting to the Macquarie University Clinical Trial Unit delegated responsibility by the study sponsor (Macquarie University) to verify that:

(a) The rights and well-being of human subjects are protected.

(b) The reported trial data are accurate, complete, and verifiable from source documents.

(c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

The monitoring activities will include:

- Verifying that the site investigators and coordinators have adequate qualifications, that resources remain adequate throughout the trial period, and that facilities, equipment, and staff are adequate to safely and properly conduct the trial.
- Verifying that the site investigators follow the approved protocol and all approved amendment(s), if any.
- Verifying that written consent was obtained for each subject participating in the trial.
- Verifying that the investigators are enrolling only eligible subjects.
- Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.
- Verifying that the investigator provides all the required reports, notifications, applications, and submissions to the HREC, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.
- Monitoring adverse events, concomitant medications and intercurrent illnesses. Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, and the HREC.
- Communicating deviations from the protocol, Standard Operating Procedures, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.
- The HREC shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research. Continuing review by the HREC routinely includes interim progress reports, as directed by the Board, review of proposed changes to research, adverse event reports, review of any protocol deviations, visits to the research site, and annual review of the research.

18. Publication of Research Findings

Publication of results of this study will be governed by the Steering Committee in accordance with the International Committee of Medical Journal Editors (ICJME) Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

19. References

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20. Samples of Forms

ALSFRS-R

MGH UMN Scale

Edinburgh Cognitive and Behavioural ALS Screen (ECAS)