A Randomized, Double-Blind, Placebo-Controlled Study, Followed by an Open-Label Extension, to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 814907 in Patients With Mild Alzheimer's Disease.

NCT03186989

25 April 2022

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# IONIS PHARMACEUTICALS, INC.

## ISIS 814907-CS1

## A Randomized, Double-Blind, Placebo-Controlled Study, Followed by an Open-Label Extension, to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 814907 in Patients with Mild Alzheimer's Disease

## Protocol Amendment 6 – 7 August 2020

## EudraCT No: 2016-002713-22


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|---|---|
| Trial Sponsor: | Ionis Pharmaceuticals, Inc.<br>2855 Gazelle Court<br>Carlsbad, CA 92010<br>Phone: + 01 760 931 9200<br>Fax: + 01 760 603 3564 |
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# ISIS 814907-CS1

**Protocol Amendment 6**

**EudraCT No: 2016-002713-22**

**Clinical Phase 1**

# A Randomized, Double-Blind, Placebo-Controlled Study, Followed by an Open-Label Extension, to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 814907 in Patients with Mild Alzheimer's Disease

**Protocol History:**

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| Original Protocol: | 19 September 2016 |
| Amendment 1: | 31 October 2016 |
| Amendment 2: | 20 December 2016 |
| Amendment 3: | 10 May 2018 |
| Amendment 4: | 1 August 2018 |
| Amendment 5: | 15 March 2019 |

**Sponsor:**
Ionis Pharmaceuticals, Inc.
Carlsbad, CA 92010

See electronic signature and date attached at end of document

[redacted]

**Confidentiality Statement**

This document contains confidential information of Ionis Pharmaceuticals, Inc. that must not be disclosed to anyone other than the recipient study staff and members of the independent ethics committee, institutional review board, or authorized regulatory agencies. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

# Protocol Signature Page

**Protocol Number:** ISIS 814907-CS1

**Protocol Title:** A Randomized, Double-Blind, Placebo-Controlled Study, Followed by an Open-Label Extension, to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 814907 in Patients with Mild Alzheimer's Disease

**Amendment:** Amendment 6

**Date:** 7 August 2020

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "A Randomized, Double-Blind, Placebo-Controlled Study, Followed by an Open-Label Extension, to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 814907 in Patients with Mild Alzheimer's Disease," dated 7 August 2020, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice (E6).

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Investigator's Signature

Investigator's Name *(please print)*

Date (DD Month YYYY)

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# PROTOCOL AMENDMENT

**Protocol Number:** ISIS 814907-CS1

**Protocol Title:** A Randomized, Double-Blind, Placebo-Controlled Study, Followed by an Open-Label Extension, to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 814907 in Patients with Mild Alzheimer's Disease

**Amendment Number:** 6

**Amendment Date:** 7 August 2020

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This amendment replaces Amendment 5 of Protocol ISIS 814907-CS1, dated 15 March 2019. The following modifications were made in this amendment.

- One MRI scan has been added during the long-term extension (LTE), Part 2 at Day 252 (or Day 336 if not performed at Day 252). The additional MRI scan during the LTE will provide further longitudinal data for safety and exploratory analyses. The Schedule of Procedures (Appendix A) has been updated to reflect the addition of the MRI scan during the LTE.
- Albumin has been added to the CSF safety labs to provide further granularity for the assessment of protein levels in CSF. The Schedule of Procedures (Appendix A) has been updated to reflect the addition of albumin.
- Concomitant therapy (Section 8.10.1) has been modified to allow antiplatelet and anticoagulant therapy with the exception of warfarin. The rationale for this change is based on review of lumbar puncture (LP) guidelines suggesting that complete discontinuation of anticoagulants or antiplatelet treatments is not required (Engelborghs et al. 2017; Horlocker et al. 2018; Dodd et al. 2018). Temporarily withholding antiplatelet and anticoagulant treatment before lumbar puncture should be considered according to local guidelines and investigator clinical judgement. Exclusion criteria (Section 5.1.2 and Section 5.2.2) regarding antiplatelet and anticoagulant therapy have been removed to reflect this change.
- Section 4.4 text updated to list the ISIS 814907 study team being unblinded to treatment assignment. Treatment assignment from Part 1 will remain blinded to investigators and patients for the duration of the study (end of LTE, Part 2).
- Appendix A.3 MAD Part1, 2-dose Regimen, Cohort D: At Week 17/D113, the three procedures listed below were inadvertently scheduled. These errors have been corrected by deleting the "X" for each of these procedures at Week 17.
    - CSF Sample for Biomarker Panel
    - CSF Samples for PK, Safety
    - Archived CSF Sample
- Appendix A.4 LTE Part 2, All Cohorts: At Week 60/D421, the procedure listed below was inadvertently not scheduled. This error has been corrected by adding an "X" at Week 60.

  - Local PT, INR, aPTT, platelets

- Appendix A.4 LTE Part 2, All Cohorts: At Week 60/D421 and Week 64 or ET/D449, the procedure listed below was inadvertently not scheduled. This error has been corrected by adding an "X" at Week 60 and Week 64 or ET.
  - PT, INR, aPTT
- Pre-dose Visit Day assessments may be performed on the dose Visit Day as a safety precaution to reduce the duration of clinic visits during the COVID-19 pandemic. Patients participating in the LTE Part 2 report to the Study Center on the Day prior to their dosing Visit Day for assessments. At the completion of assessments on the pre-dose Visit Day, patients are discharged unless the Investigator feels it is in the patient's best interest for him/her to remain in the Study Center overnight. Patients return to the Study Center on the dosing Visit Day to undergo CSF sampling and Study Drug administration.
  - Combining the pre-dose Visit Day with the dose Visit Day assessments ensures there are no missing assessments. The study assessments performed at the pre-dose Visit Day can be performed (prior to dosing) on the dosing Visit Day. Local laboratory analysis of PT, INR, aPTT, and platelets must be performed, and results reviewed prior to dosing.
  - This applies to the following visits:
    - Part 2 Long-term Extension (LTE) Treatment Evaluation Period: Day -1 and 1 (Cohorts A and B), Day 253 and 1 (Cohorts C and D), Day 84 and 85, Day 168 and 169, Day 252 and 253, Day 336 and 337.
- Overnight stay following LTE Day 1 Study Drug administration may be converted to a 6-hour visit as a safety precaution to reduce the duration of clinic visits during the COVID-19 pandemic. All assessment as planned up through 6 hours post-dose will be performed. The following safety measures have been implemented to monitor patient safety overnight:
  - Follow-up via phone calls in the evening post-dose to evaluate the patient's status. Site staff are available overnight via phone or in person if the patient requires medical attention. Sites are to notify sponsor of planned times the patient will be contacted post-discharge for Sponsor review and approval.
  - The patient's care giver must remain with the patient overnight. If the patient' travel time to the Study Center is greater than 1 hour, the study team and site will work with the patient to identify a local neurologist in case the patient experiences symptoms requiring medical attention. If the patient's travel time is less than 1 hour, the patient may return to the Study Center for medical care if needed.
  - Patient must return the next day for their Day 2 post-dose visit.
  - Assessments missed if 6-hour stay adopted: Plasma PK at 8 and 12 hours
- Minor updates and corrections have also been made to correct typographical errors and to improve the clarity of the document.

## PROTOCOL SYNOPSIS

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|---|---|
| **Protocol Title** | A Randomized, Double-Blind, Placebo-Controlled Study, Followed by an Open-Label Extension, to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 814907 in Patients with Mild Alzheimer's Disease |
| **Study Phase** | Phase 1 |
| **Indications** | Mild Alzheimer's disease (AD) |
| **Primary Objective** | To evaluate the safety and tolerability of ascending dose-levels of multiple intrathecal (IT) bolus administrations of ISIS 814907 to patients with mild AD |
| **Secondary Objective** | To characterize the cerebrospinal fluid (CSF) pharmacokinetics (PK) of ascending dose-levels of multiple IT bolus administrations of ISIS 814907 |
| **Exploratory Objectives** | To demonstrate effects of multiple IT bolus administrations of ISIS 814907 on CSF levels of total tau protein.<br><br>To explore the effects of multiple doses of ISIS 814907 on pharmacodynamic (PD) biomarkers and clinical endpoints relevant to AD.<br><br>To assess plasma PK properties of ISIS 814907. |
| **Study Design** | ISIS 814907-CS1 is a randomized, double-blinded, placebo-controlled study of multiple IT bolus administrations of ISIS 814907 in patients with mild AD aged 50-74 years.<br><br>This study is divided into 2 parts:<br><br>• Part 1: a randomized, double-blind, placebo-controlled multiple ascending dose (MAD) part, comprising a Screening Period of up to 8 weeks, a Treatment Evaluation Period of 13 weeks, and a Post-Treatment Period of 23 weeks<br><br>• Part 2: an open-label, long-term extension (LTE) part, comprising a Registration Period of up to 3 weeks (only for those who cannot transition seamlessly from Part 1 to Part 2, i.e., patients from Cohorts A and B), a Treatment Evaluation Period of 48 weeks, and a Post-Treatment Period of 16 weeks<br>o For patients participating in Cohorts A and B there will be a variable gap of time between the end of Part 1 and entry into Part 2<br>o Patients participating in Cohorts C and D will seamlessly transition from Part 1 to Part 2. Day 253 of Part 1 will correspond to Day -1 in Part 2. Dosing in Part 2 will be quarterly (i.e., with a dose interval of 84 days).<br><br>**Multiple Ascending Dose Part of Study, Part 1**<br><br>Four (4) ascending dose level cohorts (A, B, C and D) of mild AD patients will be enrolled sequentially and randomized 3:1 to receive ISIS 814907 or placebo. Cohorts A and B will comprise 8 patients each, Cohort C will comprise 12 patients and Cohort D will comprise 16 patients.<br><br>A sentinel dosing strategy will be implemented. The first 2 patients at a given dose level will be assigned 1:1 active:placebo, and at least 1 week must elapse between initiation of treatment in these 2 patients and initiation of treatment in additional patients at this dose level. The remaining patients will be assigned to active or placebo at a 5:1 ratio (cohorts with N = 8), 8:2 ratio (cohorts with N = 12), or 11:3 ratio (cohorts with N = 16) to ensure a 3:1 active:placebo balance in each cohort. During the study, PK and PD data will be compared to the ISIS 814907 levels and PD effects that are expected according to the preclinical PK/PD model. Based on these reviews, the dose level(s) and/or dosing interval for future cohort(s) may be adjusted. |

## PROTOCOL SYNOPSIS *Continued*

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| **Study Design** ***Continued*** | **Multiple Ascending Dose Part of Study, Part 1** ***Continued***<br><br>Each patient will receive 4 doses of Study Drug with a 28-day interval between doses. In the event of a dosing interval change for Cohort D, each patient will receive 2 doses of Study Drug with an 84-day interval between doses. Patients not completing the intended course of all Study Drug administrations may be replaced up to a limit of 25% of the cohort sample and only if their treatment assignments remain blinded and if the reason for premature discontinuation from the Treatment Evaluation Period does not involve a dose-limiting toxicity (DLT).<br><br>Patients in Cohorts A and B will complete all visits up to Day 253 in Part 1 and will enter Part 2 of the study after the FSMG has reviewed the Part 1 Cohort C data during the dose-escalation meeting to Cohort D; there will be a variable gap of time between the end of Part 1 and entry into Part 2 for those patients. Patients in Cohorts C and D will seamlessly transition from Part 1 into Part 2 after completing all visits up to Day 253 in Part 1. This visit will correspond to Day -1 in Part 2.<br><br>Patients who discontinue Study Drug in the Treatment Evaluation Period of Part 1 should complete any follow-up visits associated with the most recent administration of Study Drug (see Section 8.9) and should complete the Part 1 Post-Treatment Period.<br><br>**Long-Term Extension Part of Study, Part 2**<br><br>The open-label LTE part of the study will start with Cohort C completers and allow all patients completing Cohorts C and D to seamlessly transition from Part 1 to Part 2. This means that for Cohorts C and D patients Day 253 in Part 1 will correspond to Day -1 in Part 2. In Part 2, the Treatment Evaluation Period of 48 weeks will be followed by a Post-Treatment Period of 16 weeks. For Cohorts A and B patients there will be a variable gap of time between the end of Part 1 and entry into Part 2. Cohort A and B patients, who complete the Part 1 Treatment Evaluation and the Post-Treatment Periods, will be invited back to participate in Part 2. Patients who prematurely discontinue the Treatment Evaluation Period, or the Post-Treatment Period, in Part 1, and patients whose treatment assignment has been unblinded during Part 1 due to a safety issue, will not be allowed to participate in Part 2. There is no prescribed minimum or maximum interval of time required before Cohort A and B patients completing Part 1 can enter Part 2 of the study, however all Cohort A and B patients participating in the LTE, Part 2 should be enrolled in Part 2 prior to the last patient in Cohort D entering Part 2 of the study. Patients who participated in Cohorts A and B will be able to start Part 2 of the study once the FSMG has reviewed the Part 1 Cohort C data during the dose-escalation meeting to Cohort D (2/3 of patients in Cohort C having received all doses of Study Drug in Part 1) and will start the Part 2 Treatment Evaluation Period at the Cohort C dose given on a quarterly (84-day interval) basis. Dose levels and dosing regimen in the LTE, Part 2 could be adjusted in individuals or for the entire study based on ongoing review of the safety, PK/PD profile by the FSMG and the Sponsor. All patients in Part 2 will receive ISIS 814907.<br><br>Patients who prematurely discontinue the Treatment Evaluation Period in Part 2 should complete any follow-up visits associated with the most recent administration of ISIS 814907 (see Section 8.9) and should complete the Part 2 Post-Treatment Period. |
| **Number of Patients** | Approximately 44 patients will be randomized in the MAD, Part 1 of the study.<br><br>The number of patients randomized may be higher if some patients need to be replaced, the sizes of the cohorts are expanded to obtain further experience with particular dose levels and/or additional cohorts are added. A maximum of 64 patients may be randomized.<br><br>The number of patients entering the LTE, Part 2 of the study will be equal or less than the number of patients enrolled in Part 1. |

## PROTOCOL SYNOPSIS *Continued*

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| **Study Population** | **Inclusion Criteria for Multiple Ascending Dose, Part 1**<br>Patients must meet the following inclusion criteria to be eligible:<br>*Target Population*<br>1. Patient is able to read, understand, and provide written informed consent (signed and dated)<br>2. Male or female, aged 50-74 years, inclusive, at Screening<br>3. AD of mild severity (CDR Global score of 1 or CDR Global Score of 0.5 with a Memory score of 1; MMSE 20-27, inclusive) at Screening<br>4. Reduced CSF Aβ42 at Screening, consistent with a diagnosis of mild AD<br>5. Elevated CSF total tau and p-tau at Screening, consistent with a diagnosis of mild AD<br>6. Diagnosis of probable AD dementia based on National Institute of Aging-Alzheimer Association (NIA-AA) criteria (may be either amnestic [Global CDR score of 0.5 of 1.0] or nonamnestic [Global CDR score of 1.0] presentation) at Screening<br>7. Body Mass Index (BMI) ≥ 18 and ≤ 35 kg/$m^2$<br>8. Total body weight > 50 kg (110 lbs)<br>9. Able and willing to meet all study requirements, including travel to Study Center, procedures, measurements and visits, including:<br>a. Reside in a proximity to the Study Center that permits prompt appearance at the facility if requested by the Investigator (maximum of 4-hour travel to Study Center), unless neurological examination or admission, if needed, can be arranged promptly at a suitably equipped and staffed alternative facility and these arrangements have been discussed and agreed to by the Ionis Medical Monitor<br>b. Adequately supportive psychosocial circumstances, in the opinion of the Investigator<br>c. Caregiver/trial partner committed to facilitate patient's involvement in the study who is reliable, competent, at least 18 years of age, willing to accompany the participant to select study visits and to be available to the Study Center by phone if needed and who, in the opinion of the Investigator, is and will remain sufficiently knowledgeable of the patient's ongoing condition to respond to Study Center inquiries about the patient, such as providing information related to study outcome measures requiring caregiver input<br>d. Adequate visual and auditory acuity for neuropsychological testing<br>10. Able to read at a level necessary to complete study assessments<br>11. No evidence or prior diagnosis of general learning disability<br>*Reproductive Status*<br>12. Females must be non-pregnant, non-lactating and either surgically sterile (e.g., bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or post-menopausal (defined as 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the post-menopausal range for the laboratory involved)<br>13. Males must be surgically sterile, abstinent* or, if engaged in sexual relations with a female of child-bearing potential, must agree to use an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (ISIS 814907 or placebo) or end of the study, whichever is longer<br>* Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception. |

## PROTOCOL SYNOPSIS *Continued*

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| **Study Population** ***Continued*** | **Exclusion Criteria for Multiple Ascending Dose, Part 1**<br>Patients meeting any of the following criteria are not eligible for the study:<br>*Target Disease Exceptions*<br>1. First or second degree family member among the investigational or Sponsor staff directly involved in the trial<br>2. Any contraindication or unwillingness to undergo MRI scanning (e.g., metal implants including MRI incompatible IUDs, claustrophobia, agitation or tremor of a severity that precludes MRI scans)<br>3. Any contraindication or unwillingness to undergo a lumbar puncture (LP)<br>*Medical History and Concurrent Disease*<br>4. Patient receives daily nursing care due to cognitive condition<br>5. Evidence of clinically relevant neurological disease other than the disease being studied, including<br>a. Cerebrovascular disease (history of TIA, stroke, significant vascular disease [large vessel stroke, diffuse white matter hyperintensities {WMHs}, multiple lacunes, bilateral thalamic lesions, and/or > 5 microhemorrhages on brain MRI] or modified 8-item Hachinski Ischemia Scale score ≥ 4)<br>i. In addition to microhemorrhages, the degree of WMH severity will be centrally rated on T2 FLAIR and GRE T2 star images using the Age Related White Matter Changes (ARWMC) scale (e.g., WMHs > 5 mm, rated on a 4-point scale ranging from 0 (no lesions) to 3 (diffuse involvement of the entire region), within 5 regions in each hemisphere; a score of 3 in a region constitutes the presence of diffuse WMH)<br>ii. Multiple lacunes are rated as the presence of at least 2 lacunes in the basal ganglia and at least 2 lacunes in the frontal white matter. To meet the criterion for the presence of bilateral thalamic lesions, at least 1 lesion must to be present in each thalamus.<br>b. Current infectious/metabolic/systemic diseases affecting CNS<br>c. History of a serious infectious disease affecting the brain in the 5 years prior to Screening<br>d. History of clinically significant head trauma (i.e., any loss of consciousness for > 5 minutes), including motor vehicle accident and/or concussion in the 3 years prior to Screening<br>e. MRI scan at Screening shows evidence for a potential alternative etiology for dementia (i.e., non-AD etiology)<br>f. History of generalized seizures in the 3 years prior to Screening<br>6. Psychiatric diagnosis/symptoms interfering with assessment of cognition<br>a. Attempted suicide, suicidal ideation with a plan that required hospital admission and/or change in level of care within 6 months prior to Screening. For patients with (i) a suicide ideation score ≥ 4 on the Columbia Suicide Severity Rating Scale (C-SSRS) within the last 6 months, or (ii) suicidal behaviors within the last 6 months (as measured by the answer “Yes” on any of the C-SSRS Suicidal Behavior Items, a risk assessment should be done by an appropriately-qualified mental health professional (e.g., a Psychiatrist or licensed Clinical Psychologist) to assess whether it is safe for the patient to participate in the study. Patients deemed by the Investigator to be at significant risk of suicide should be excluded<br>b. Major depressive episode within 6 months prior to Screening (with the exception of patients in remission on allowed concomitant antidepressant medication) or at risk for psychosis, confusional state or violent behavior in the opinion of the Investigator<br>c. Geriatric Depression Scale Short Form > 6<br>d. History of alcohol or drug dependency/abuse within 3 years prior to Screening |

## PROTOCOL SYNOPSIS *Continued*

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| **Study Population** ***Continued*** | *Medical History and Concurrent Disease Continued*<br>7. Clinically significant cardiac conditions including cardiac failure, angina or previous acute coronary syndrome within 6 months of Screening<br>8. Ongoing or recent (within 12 weeks of Screening) uncontrolled, clinically significant medical condition including:<br>a. Hematological, hepatic, diabetes, hypertension, thyroid or endocrine disease, gastrointestinal disease, dialysis, or abnormal renal function<br>b. Retinal impairment or disease that would interfere with the ability to comply with study procedures<br>c. Peripheral vascular disease that would interfere with the ability to comply with study procedures<br>d. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C, chronic hepatitis B consistent with CDC interpretation of serology panel or syphilis<br>9. History of bleeding diathesis or coagulopathy and/or platelet count < LLN at Screening<br>10. A medical history of brain or spinal abnormalities by MRI/CT or history that might interfere with the LP process, CSF circulation or safety assessment, including subarachnoid hemorrhage, suggestions of raised intracranial pressure on MRI or ophthalmic examination, spinal stenosis or curvature, spina bifida occulta, Chiari malformation, hydrocephalus, syringomyelia, tethered spinal cord syndrome, frontotemporal brain sagging syndrome and connective tissue disorders such as Ehlers-Danlos syndrome and Marfan syndrome<br>11. Any medical condition that increases risk of meningitis unless patient is receiving appropriate prophylactic treatment<br>12. History of malignancy within 5 years prior to Screening, except for adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, localized prostate carcinoma. Patients with other malignancies that have been treated with potentially curative therapy with no evidence of recurrence for ≥ 5 years post-therapy may also be eligible if approved by the Sponsor Medical Monitor<br>13. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed 3 days prior to Part 1, Day -1<br>14. At Screening, have any condition such as medical, psychiatric or neurological other than the tauopathy under study which, in the opinion of the Investigator or Sponsor, would make the patient unsuitable for inclusion or could interfere with the patient participating in or completing the study<br>*Prohibited and Restricted Medications and Procedures*<br>15. Treatment with another investigational product (drug, biological agent or device) within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer<br>16. Use of a disallowed CNS-active or antipsychotic medication within 4 weeks or 5 half-lives (whichever is greater) prior to the start of Screening<br>17. Change in dose regimen of an allowed CNS-active or antipsychotic medication within 4 weeks or 5 half-lives (whichever is greater) prior to the start of Screening<br>18. Change in dose regimen of a cholinesterase inhibitor or memantine within 8 weeks prior to the start of Screening<br>19. Change in dose regimen of estrogen replacement therapy within 4 weeks prior to the start of Screening<br>20. Change in dose regimen of nutraceuticals or supplements within 4 weeks prior to the start of Screening |

## PROTOCOL SYNOPSIS *Continued*

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|---|---|
| **Study Population** ***Continued*** | *Prohibited and Restricted Medications and Procedures Continued*<br><br>21. Use of warfarin<br>22. Use of Neudexta (dextromethorphan and quinidine)<br>23. Prior treatment with an active immunotherapy agent targeting the CNS<br>24. Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter<br>25. Any medical or surgical procedure involving general anesthesia within 12 weeks of Screening or planned during the study<br>26. Any history of gene therapy or cell transplantation or any experimental brain surgery<br>*Physical and Laboratory Findings*<br>27. Clinically significant laboratory, vital sign or ECG abnormalities at Screening (including HR < 45 bpm, SBP < 90 mmHg and confirmed BP readings > 170/105 mmHg)<br>28. Any hepatic, glucose, renal, hematology or thyroid laboratory tests above or below the limits of normal that are considered to be clinically significant must be discussed with the Sponsor Medical Monitor<br>29. Clinically significant B12 or folate deficiencies at Screening or previous deficiencies that have not been corrected for at least 12 weeks prior to Screening<br>**Inclusion Criteria for Long-Term Extension, Part 2**<br>*This section is only applicable to patients from Cohorts A and B, as patients from Cohort C and D will seamlessly transition to Part 2*.<br>Patients from Cohorts A and B must meet the following inclusion criteria to be eligible:<br>*Target Population*<br>1. Able to read, understand, and provide written informed consent (signed and dated)<br>2. Able and willing to meet all study requirements in the opinion of the Investigator, including:<br>a. Adequately supportive psychosocial circumstances<br>b. Caregiver/trial partner committed to facilitate patient's involvement in the study who is reliable, competent, at least 18 years of age, willing to accompany the participant to select study visits, and to be available to the Study Center by phone if needed, and who, in the opinion of the Investigator, is and will remain sufficiently knowledgeable of the patient's ongoing condition to respond to Study Center inquiries about the patient, such as providing information related to study outcome measures requiring caregiver input<br>c. Adequate visual and auditory acuity for neuropsychological testing<br>d. Able to tolerate blood draws and lumbar punctures<br>3. Must have completed the Treatment Evaluation and Post-Treatment Periods in MAD, Part 1 of the study |

## PROTOCOL SYNOPSIS *Continued*

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| **Study Population** ***Continued*** | *Reproductive Status*<br>4. Females must be non-pregnant, non-lactating and either surgically sterile (e.g. bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or post-menopausal (defined as 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the post-menopausal range for the laboratory involved)<br>5. Males must be surgically sterile, abstinent*, or if engaged in sexual relations with a female of child-bearing potential, must agree to use and acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of ISIS 814907 or end of study, whichever is longer.<br>* Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception.<br>**Exclusion Criteria for Long-Term Extension, Part 2**<br>*This section is only applicable to patients from Cohorts A and B, as patients from Cohort C and D will seamlessly transition to Part 2.*<br>*Prohibited and restricted Medications and Procedures*<br>1. Treatment with another investigational product (drug, biological agent, or device) within 1 month of Registration, or 5 half-lives of investigation agent, whichever is longer<br>2. Use of a disallowed CNS-active or antipsychotic medication within 4 weeks or 5 half-lives (whichever is greater) prior to Registration<br>3. Change in dosing regimen of an allowed CNS-active or antipsychotic medication within 4 weeks or 5 half-lives (whichever is greater) prior to Registration<br>4. Change in dose regimen of a cholinesterase inhibitor or memantine within 8 weeks prior to Registration<br>5. Change in dose regimen of estrogen replacement therapy within 4 weeks prior to Registration<br>6. Change in dose regimen of nutraceuticals or supplements within 4 weeks prior to Registration<br>7. Use of warfarin<br>8. Use of Neudexta (dextromethorphan and quinidine)<br>9. Prior treatment with an active immunotherapy agent targeting the CNS<br>10. Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter<br>11. Any medical or surgical procedure involving general anesthesia within 12 weeks of Registration or planned during the study<br>12. Any history of gene therapy or cell transplantation or any experimental brain surgery<br>*Medical History and Concurrent Disease*<br>13. Have any other condition which, in the opinion of the Investigator or Sponsor, would make the patient unsuitable for the inclusion or could interfere with the patient participating in or completing the study |

## PROTOCOL SYNOPSIS *Continued*

**Treatment Groups**

**Multiple Ascending Dose, Part 1**

ISIS 814907, placebo

Patients will receive 4 IT bolus doses of Study Drug at monthly (28-day) intervals during the 3-month Treatment Evaluation Period (on Days 1, 29, 57, and 85).

In the event of a dosing interval change, patients in Cohort D could receive 2 IT bolus doses of Study Drug at quarterly (84-day) interval during the 3-month Treatment Evaluation Period (on Days 1 and 85).

For patients who receive ISIS 814907, planned total dose is shown in the table below.

| Planned Dose of Active Study Drug | # of Doses | Total ISIS 814907 |
|---|---|---|
| Cohort A: 10 mg ISIS 814907, monthly | 4 | 40 mg |
| Cohort B: 30 mg ISIS 814907, monthly | 4 | 120 mg |
| Cohort C: 60 mg ISIS 814907, monthly | 4 | 240 mg |
| Cohort D: 90 mg ISIS 814907, monthly | 4 | 360 mg |
| *or*<br>Cohort D: 115 mg ISIS 814907, quarterly | 2 | 230 mg |

**Long-Term Extension, Part 2**

ISIS 814907

Patients will receive IT bolus doses of ISIS 814907 at quarterly (84-day) intervals for a total of 5 doses over the 48-week Treatment Evaluation Period (on Days 1, 85, 169, 253, and 337).

Patients who were randomized to Cohort C in Part 1 will continue Part 2 at the Cohort C dose; similarly, patients who were randomized to Cohort D in Part 1 will continue Part 2 at the Cohort D dose. Cohort A and B patients will start Part 2 of the study at the Cohort C dose. Dose levels and dosing regimen in the LTE could be adjusted in individuals or for the entire study based on ongoing review of the safety, PK/PD profile by the FSMG and the Sponsor.

| Planned Dose of Active Study Drug | # of Doses | Total ISIS 814907 |
|---|---|---|
| Patients transitioning from Cohorts A, B, and C:<br>60 mg ISIS 814907, quarterly | 5 | 300 mg |
| Patients transitioning from Cohort D:<br>90 mg ISIS 814907, quarterly | 5 | 450 mg |
| *or*<br>Patients transitioning from Cohort D:<br>115 mg ISIS 814907, quarterly | 5 | 575 mg |

## PROTOCOL SYNOPSIS *Continued*

| | |
|---|---|
| **Study Drug Dosage and Administration** | Throughout the study, each dose of ISIS 814907 or placebo will be administered as a single 20 mL IT bolus injection.<br><br>Administration will be via lumbar puncture (LP) using a small gauge needle inserted into the L3/L4 space, although placement at a different level (either in the space above or the space below) is allowed if patient anatomy or clinical judgment dictates.<br><br>Depending on institutional guidelines, local anesthesia may be used for the procedure. Sedation is not permitted. Spinal ultrasound may be used for the LP procedure, if deemed necessary, but is not required. Fluoroscopy guidance may be used if attempts at lumbar puncture without imaging are unsuccessful.<br><br>Dosing instructions and details regarding administration will be provided in the Study Drug Manual. The study team, including the site pharmacist, will be blinded to treatment assignment in Part 1. Part 2 is open-label and all patients will receive ISIS 814907. However, the treatment assignments from Part 1 will remain blinded for the duration of the study. |
| **Dosing of Individual Patients and Dose Escalation of Cohorts** | *Continued Dosing in an Individual Patient Throughout the Study*<br><br>If there are no significant safety issues related to Study Drug (i.e., DLTs) in an individual patient in the time interval between the last and the next dose, then the next dose administration for that patient can proceed.<br><br>All serious adverse events (SAEs) and severe adverse events (AEs) will be reviewed by the Formal Safety Monitoring Group (FSMG), whose team members may be unblinded. If a patient experiences an AE between doses that the Investigator suspects to be a DLT, further dosing in the patient cannot proceed until the FSMG completes safety evaluations and the Investigator has received written approval from the Sponsor to resume dosing. If the Investigator is uncertain whether an AE that is neither serious nor severe constitutes a significant safety issue, the decision to proceed to the next dose administration for that patient will be referred to the FSMG via the Ionis Medical Monitor.<br><br>If a suspected DLT occurs *during* IT injection of the Study Drug, administration of Study Drug to the patient must be stopped (i.e., the injection must be immediately discontinued); and, if the event is determined to be a DLT, no further Study Drug injections may be administered in this patient. The Investigator must contact the Medical Monitor as soon as possible to discuss the case. The FSMG should determine if any relevant findings have been observed in other patients in the study.<br><br>*Cohort-to-Cohort Dose Escalation Algorithm in MAD, Part 1*<br><br>Four (4) ascending-dose cohorts (Cohorts A, B, C, and D) will be enrolled sequentially. In each cohort, patients will receive 4 doses of Study Drug at 28-day intervals, unless a dosing interval change for Cohort D, is deemed appropriate by the FSMG. In the event of a dosing interval change, patients in Cohort D would receive 2 doses of Study Drug with an 84-day interval.<br><br>The progression of the study from one cohort to the next will be determined by the FSMG and will generally be based on the number of DLTs observed in patients treated with ISIS 814907 as well as review of the PK and PD data collected in the study. The FSMG can recommend initiation of dosing in the next cohort when 2 conditions have been met: (i) at least 2/3 of the patients in the lower-dose cohort have been followed for at least 7 days after receipt of the fourth dose of Study Drug and (ii) all available safety, PK and PD results for all patients enrolled in lower-dose cohorts have been reviewed by the FSMG. Based on the PD and PK results, the FSMG has the discretion to adjust the dose from one cohort to the next as outlined in the 'Rationale for Dose and Schedule Selection'; they also can adjust the dosing interval from 4 doses with a 28-day interval to 2 doses with an 84-day interval over 3 months in Cohort D. The occurrence of DLTs in 2 patients in a cohort will result in the dose for that cohort being dose limiting in this study. Progression to the next cohort will occur only after the FSMG has recommended initiation of dosing in that cohort and the prior cohort has completed enrollment. |

## PROTOCOL SYNOPSIS *Continued*

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|---|---|
| **Dosing of Individual Patients and Dose Escalation of Cohorts** ***Continued*** | *Dose-Limiting Toxicity in MAD, Part 1*<br><br>In this study, a suspected DLT is defined as an adverse event (AE) that, in the judgment of a Site Investigator, is of sufficient significance to be dose limiting, is possibly or definitely related to Study Drug (i.e., the AE is substantially less likely to occur in patients not administered the Study Drug) and that it is not a known: (i) sign or symptom of AD (with the exception of acute disease worsening that is inconsistent with the patient's prior disease course), (ii) effect of the LP injection procedure or (iii) effect of any other study procedure (e.g., venipuncture, MRI scan).<br><br>If an Investigator considers an event to be a suspected DLT, the event will be referred to the unblinded FSMG which will determine whether it constitutes a DLT. No further dosing may occur in any patient while the FSMG reviews the event.<br><br>If a single DLT is encountered in a cohort, the cohort may be expanded by up to 100% to assess safety at that dose. If dosing in higher dose cohort(s) is ongoing at the time that a single DLT is encountered in a lower dose cohort, further enrollment in the higher dose cohort(s) will stop until (1) all current patients have completed dosing and at least 7 days of post-treatment safety evaluations from the last dose and (2) the FSMG has reviewed these data. In addition, in the event of a single DLT, the FSMG will decide if further measures are required such as pausing or reducing the dose in ongoing patients in the higher dose cohort(s). Enrollment in higher-dose cohorts will not resume until the FSMG has conducted these additional reviews.<br><br>The occurrence of a DLT in 2 patients in a cohort will result in termination of further dosing in that cohort and any higher-dose cohort that is also ongoing. The occurrence of one SAE or two severe AEs in a cohort will also result in termination of further dosing in that cohort and in any higher-dose cohort that is ongoing, provided the event is considered by the Investigator and Sponsor to be at least possibly related to Study Drug, the event is not an SAE where the only seriousness criterion is hospitalization if the hospitalization was only for observation and no specific treatment was administered for the event leading to hospitalization, and the event is not a known: (i) sign or symptom of AD (with the exception of acute disease worsening that is inconsistent with the patient's prior disease course), (ii) effect of the LP injection procedure or (iii) effect of any other study procedure (e.g., venipuncture, MRI scan). In these situations, the Sponsor and FSMG will determine if enrollment of additional patients at the previous (lower) tolerated dose or enrollment of a new cohort of patients at an alternative dose is required to conclude that a given dose is the MTD.<br><br>*Adjustment of Dose in LTE, Part 2*<br><br>Patients who were enrolled in Cohort C in Part 1 will continue Part 2 at the Cohort C dose; similarly, patients who were enrolled in Cohort D in Part 1 will continue Part 2 at the Cohort D dose. Cohort A and B patients will start Part 2 of the study at the Cohort C dose. Dose levels and dosing regimen in the LTE, Part 2 could be adjusted in individuals or for the entire study based on ongoing review of the safety, PK/PD profile by the FSMG and the Sponsor.<br><br>*Dose-Limiting Toxicity in LTE, Part 2*<br><br>If an Investigator considers an event to be a suspected DLT, the event will be referred to the unblinded FSMG which will determine whether it constitutes a DLT. No further dosing may occur in any patients while the FSMG reviews the event.<br><br>The unblinded FSMG consists of at least 3 medical doctors experienced in the conduct of clinical studies in patients with neurodegenerative diseases. The FSMG will review subjects' available blinded data, including AEs and SAEs, vital signs, physical and neurological examinations, electrocardiograms (ECGs), clinical laboratory safety tests, and PD assessments. Review of blinded data may be followed by review of unblinded data of the current cohort and preceding cohorts. The decisions of the FSMG will be recorded in minutes of the meeting. The FSMG responsibilities will be defined in a charter. Methods by which the study team will remain blinded will be described in the charter. |

## PROTOCOL SYNOPSIS *Continued*

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|---|---|
| **Rationale for Dose and Schedule Selection** | **Multiple Ascending Dose, Part 1**<br>The initial dose levels for this study are based on preclinical safety and the no adverse effect level (NOAEL) for ISIS 814907. The lowest planned dose of 10 mg (40 mg cumulative over 3 months) is 35-fold (44-fold cumulative) lower than the NOAEL of 350 mg (1750 mg cumulative over 3 months). The highest planned dose of 115 mg given twice over 3 months (230 mg cumulative over 3 months) is 3-fold (7-fold cumulative) lower than the NOAEL established in preclinical toxicology program.<br>[redacted]<br>CSF samples for PK analysis and measurement of total tau protein will be collected prior to each dose and during the Post-Treatment Period. These measurements will be compared to those predicted from preclinical data. The dosing interval and the doses utilized in later ascending-dose cohorts may be adjusted, and/or additional cohorts of patients may be added, if necessary to achieve pharmacologically-relevant levels of drug in the brain based on preclinical models and data from earlier cohorts. Based on the review of the data from previous cohorts, a change in dosing interval may be advised by the FSMG to assess the suitability of quarterly dosing in patients. The maximum dose increment for the 4-dose regimen (4 doses over 3 months) design is as follows: From Cohort A to Cohort B, the increment can be no more than 3x; for all subsequent escalations, the increment from the current cohort to the next cannot be more than 2x the current dose level. The maximum dose tested in a cohort will not exceed 115 mg. When transitioning to a cohort with a new dose interval, the total dose of the 2-dose regimen (2 doses over 3 months) will not exceed the total dose of the previous 4-dose regimen cohort. |

## PROTOCOL SYNOPSIS *Continued*

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|---|---|
| **Rationale for Dose and Schedule Selection** ***Continued*** | **Long-Term Extension, Part 2**<br><br>The aim of Part 2 is to evaluate the safety, PK and PD effects of a quarterly (84-day) dose interval of two dose levels of ISIS 814907. Cohort C patients will seamlessly transition to Part 2 after completing Part 1, and they will continue the Cohort C dose with a quarterly dose interval in the LTE, Part 2. Cohort D patients will also seamlessly transition to Part 2 after completing Part 1, and they will continue the Cohort D dose with a quarterly dose interval in the LTE, Part 2. Cohort A and B patients who have completed the Treatment Evaluation and Post-Treatment Periods in Part 1 are also eligible to enter Part 2 of the study. They will start Part 2 at the Cohort C dose with a quarterly dose interval, if permitted by the FSMG review of the Cohort C package for the dose-escalation meeting to Cohort D (2/3 of patients in Cohort C having received all doses of Study Drug in Part 1). Patients entering the LTE Part 2 will be maintained on the dose they received when they initiated Part 2. Dose levels and dosing regimen in the LTE could be adjusted in individuals or for the entire study based on ongoing review of the safety, PK/PD profile by the FSMG and the Sponsor.<br><br>Depending on safety and PK/PD data emerging from the entire study, including the LTE, the FSMG and Sponsor may decide to adjust the Part 2 dose and/or dosing regimen in some or all patients to a new dose level that is thought likely to be an optimal therapeutic dose level and that does not exceed a dose of 115 mg. |
| **Study Visit Schedule and Procedures** | **Multiple Ascending Dose, Part 1**<br><br>After informed consent is obtained, patients will undergo a Screening evaluation during an 8-week period. Patients who meet the eligibility criteria will visit the Study Center on Day -1 to undergo clinical, blood, and ECG evaluations. On Day 1, patients will be admitted to the Study Center, undergo pre-dose evaluations of vital signs and then receive an IT bolus injection of ISIS 814907 or placebo (3:1 overall in each cohort). Following the initial LP injection on Day 1, patients will be kept at the Study Center for at least 24 hours and carefully monitored for any adverse clinical symptoms or signs. This inpatient post-dose assessment may be reduced to a minimum of 6 hours following the 2nd, 3rd, and 4th dose administrations provided a visit is made to the Study Center the next day. Assessments during these admission periods include neurological and physical examination, vital signs, ECGs, blood sampling, and clinical laboratory analyses. Full standard neurological assessment (including fundi) will be performed 3 hours after dosing and prior to discharge from the Study Center.<br><br>Study Drug administration will take place on Days 1, 29, 57, and 85. During the Treatment Evaluation Period, Study Center visits are held on Days -1, 1, 2, 8, 28, 29, 30, 36, 56, 57, 58, 84, 85, and 86. Under the 2-dose regimen, Study Drug administration will take place on Days 1 and 85, and Study Center visits are held on Days -1, 1, 2, 8, 29, 57, 84, 85, and 86.<br><br>During the Post-Treatment Period, patients will visit the Study Center on Days 113, 141, 169, 197 (patients in Cohort C and D only), and 253.<br><br>In addition, the Study Center will monitor the patient's condition through telephone contact on Days 3, 31, 59, 64, 87, and 92 during the 4-dose regimen and on Days 3, 87, and 92 during the 2-dose regimen.<br><br>CSF samples (approximately 20 mL each) will be taken pre-dose on each Study Drug administration day during the Treatment Evaluation Period (Days 1, 29, 57, and 85 under the 4-dose regimen, or Days 1 and 85 under the 2-dose regimen) and during the Post-Treatment Period. These samples will be utilized for PK, tau protein, and other biomarker and laboratory analyses. In the Post-Treatment Period, CSF samples (approximately 20 mL) will be taken at Days 113 and 141 in Cohorts A and B, and at Days 141 and 197 in Cohorts C and D for additional evaluation of PK, tau protein, and other biomarkers. |

## PROTOCOL SYNOPSIS *Continued*

| | |
|---|---|
| **Study Visit Schedule and Procedures** ***Continued*** | **Multiple Ascending Dose, Part 1** ***Continued***<br><br>If a patient terminates early from the Treatment Evaluation Period of Part 1, he/she will be encouraged to return for the near-term follow-up visits associated with the most recent dose of Study Drug and for the Post-Treatment Period (Days 113-253).<br><br>**Long-Term Extension, Part 2**<br><br>Patients from Cohorts A and B returning to participate in the LTE: after informed consent is obtained, eligibility for entry into Part 2 will be evaluated during the Registration Visit.<br><br>Patients from Cohorts C and D transitioning seamlessly from Part 1 into Part 2: there will be no Registration Visit during which eligibility needs to be reviewed, as eligibility was assessed at the start of Part 1 during Screening. Part 1, Day 253 will coincide with Part 2, Day -1 for all patients who transition seamlessly. All assessments listed in both the Part 1, Day 253 visit and the Part 2, Day -1 visit must be completed at this visit.<br><br>On Part 2, Day 1, patients will be admitted to the Study Center, undergo pre-dose evaluations of vital signs and receive an IT bolus injection of ISIS 814907. All patients entering Part 2 must be kept at the Study Center for at least 24 hours following the first ISIS 814907 administration and undergo safety monitoring as scheduled. This 24-hour safety monitoring is required as it will not be known which patients received placebo in Part 1 and are therefore receiving ISIS 814907 for the first time in Part 2. For all subsequent administrations of ISIS 814907 in Part 2, the inpatient post-dose assessments may be reduced to a minimum of 6 hours. Assessments during these admission periods include neurological and physical examinations, vital signs, ECGs, blood sampling, and clinical laboratory analyses. Full standard neurological assessment (including fundi) will be performed 3 hours after dosing and prior to discharge from the Study Center.<br><br>ISIS 814907 administration in Part 2 will take place on Days 1, 85, 169, 253, and 337. During the Part 2 Treatment Evaluation Period, the patients will visit the Study Center at the times listed in the Schedule of Procedures – Part 2 (Appendix A). The Study Center will also monitor the patient's condition through scheduled telephone calls between visits.<br><br>CSF samples (approximately 20 mL each) will be taken pre-dose on each ISIS 814907 administration day during the Treatment Evaluation Period (Days 1, 85, 169, 253, and 337) and on Day 421 in the Post-Treatment Period. These CSF samples will be utilized for assessments of PK, tau protein, and other biomarker and laboratory analyses.<br><br>If a patient terminates early from the Part 2 Treatment Evaluation Period, he/she will be encouraged to return for the follow-up visits associated with their most recent administration of ISIS 814907 and for the Post-Treatment Period (Days 421-449). |

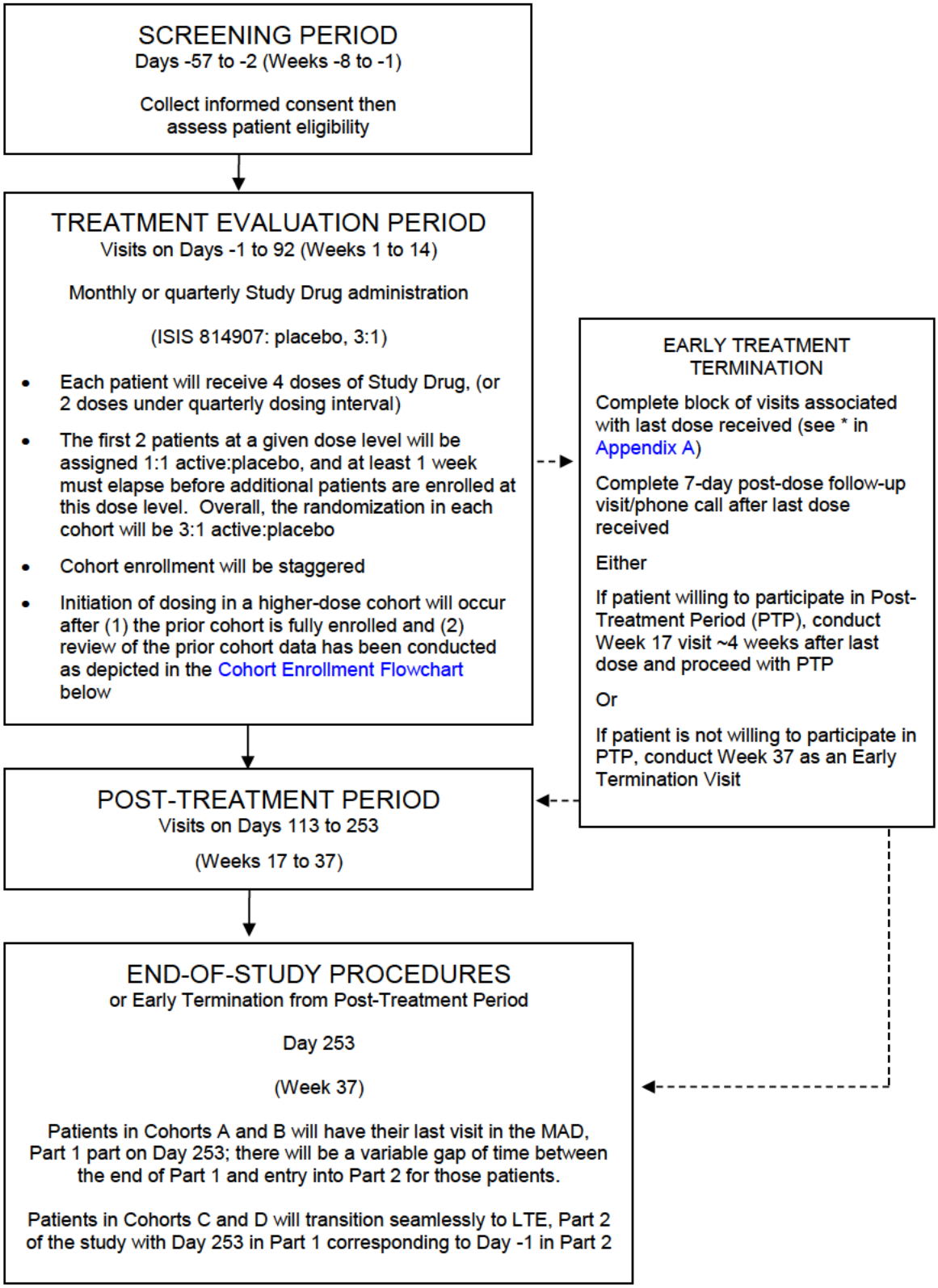
## PROTOCOL SYNOPSIS *Continued*

| | |
|---|---|
| **Safety and Tolerability Evaluations** | Patient safety will be monitored closely during the study by the Investigator and the FSMG. Further oversight of compliance with study safety procedures will be provided by the Ionis Medical Monitor.<br>Safety and tolerability evaluations include:<br>• Physical examination and standard neurological assessment (including fundi)<br>• Vital signs (HR, BP, orthostatic changes, weight)<br>• ECG<br>• AEs and concomitant medications<br>• Columbia Suicide Severity Rating Scale (C-SSRS)<br>• CSF safety labs (cell counts, protein, glucose)<br>• Plasma laboratory tests (clinical chemistry, hematology)<br>• Urinalysis<br>• Neuroimaging assessments will be conducted using a 3T MRI scanner, and safety scans must be reviewed locally by a trained neuroradiologist:<br>  ○ Safety MRI sequences (GRE T2 star, T2 FLAIR, T2 FSE/TSE, DTI) at Screening and Day 169 in Part 1, and at the Registration Visit (patients who are not seamlessly transitioning only), Day 252 (or Day 336 if not performed at Day 252) and Day 449 in Part 2<br>• Clinical and volumetric neuroimaging measures will be used to monitor for unexpected deterioration. |
| **Pharmacokinetic Evaluations** | **Multiple Ascending Dose, Part 1**<br>A CSF sample will be collected pre-dose on each Study Drug administration day during the Treatment Evaluation Period (Days 1, 29, 57, and 85 under the 4-dose regimen, or Days 1 and 85 under the 2-dose regimen) and during the Post-Treatment Period (Days 113 and 141 for patients in Cohorts A and B, and Days 141 and 197 for patients in Cohorts C and D) for PK and PD analyses. The ISIS 814907 half-life in CSF will be calculated, if possible.<br>In addition, plasma samples will be collected throughout the study as shown in the PK Sampling Schedule – Part 1 (Appendix C).<br>Plasma post-distribution drug levels will be measured. $C_{max}$ and AUC will be determined, and elimination half-life will be assessed where appropriate.<br>**Long-term Extension, Part 2**<br>A CSF sample will be collected pre-dose on each ISIS 814907 administration day during the Treatment Evaluation Period (Days 1, 85, 169, 253, and 337) and on Day 421 of the Post-Treatment Period for PK and PD analyses.<br>In addition, plasma samples will be collected throughout the study as shown in the PK Sampling Schedule – Part 2 (Appendix C).<br>Plasma post-distribution drug levels will be measured. $C_{max}$ and AUC will be determined. |

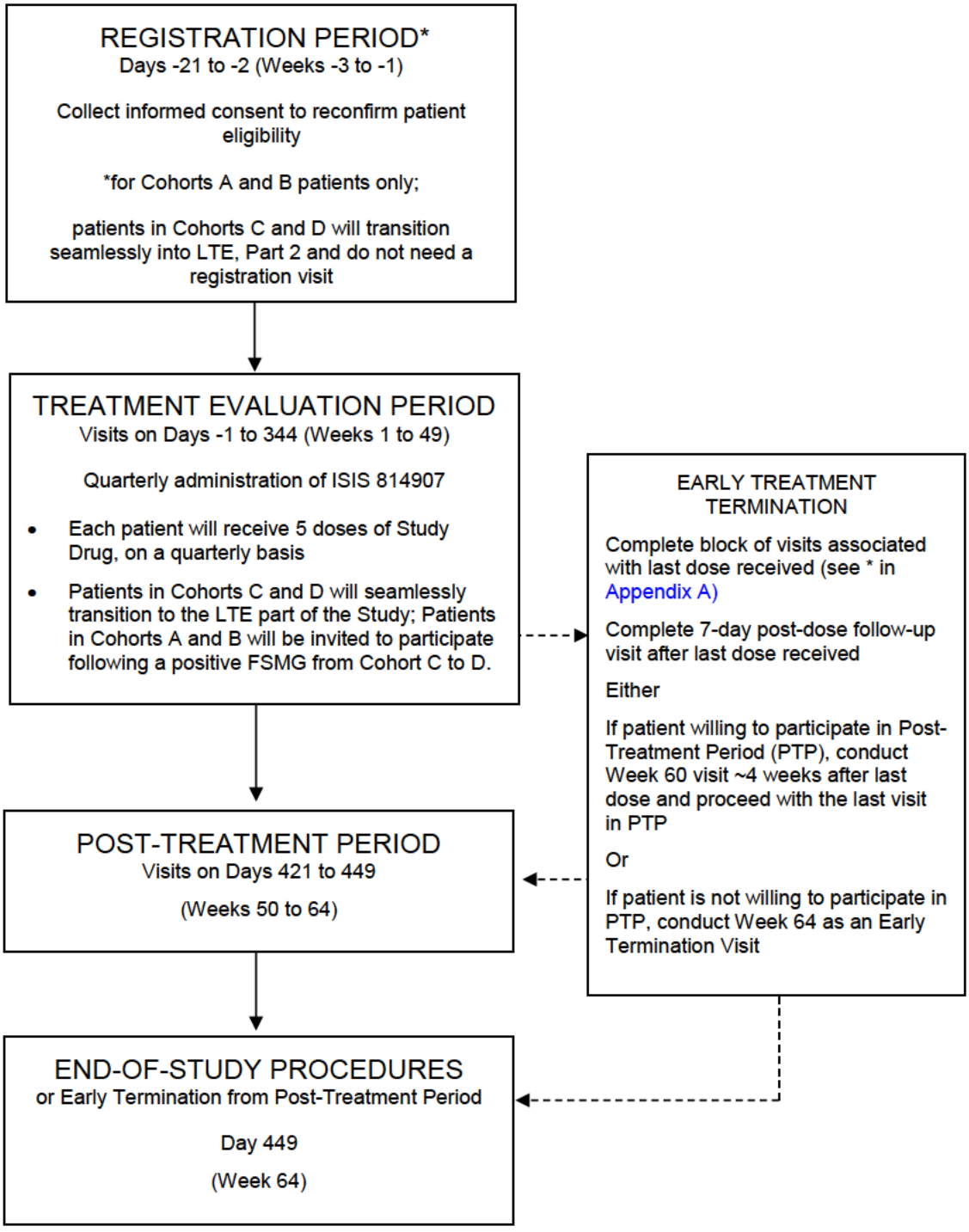
## PROTOCOL SYNOPSIS *Continued*

| | |
|---|---|
| **Exploratory Evaluations** | Parameters include:<br>• Biochemical<br>  ○ Potential CSF and blood/plasma biomarkers include, but are not limited to neuronal and synaptic injury markers, innate immune activation markers, complement components and lipid-related biomarkers<br>• Neuroimaging<br>  ○ Structural MRI (hippocampal, whole brain and ventricular volumes)<br>  ○ Arterial Spin Labelling (ASL)<br>  ○ PET (Cohorts C and D only in Part 1, and all patients in Part 2)<br>• Functioning/ability to perform activities of daily living<br>  ○ Functional Activities Questionnaire (FAQ)<br>• Cognitive<br>  ○ Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)<br>  ○ Mini-mental state examination (MMSE)<br>• Neuropsychiatric<br>  ○ Neuropsychiatric Inventory – Questionnaire (NPI-Q)<br>Analyses may explore the relationship between parameters and genetic causes of AD (*APP, PSEN1, PSEN2*) or potential genetic modifiers of disease phenotype (commonly occurring risk-associated SNPs of *APOE, BCHE, IL1RAP* and *MAPT H1* haplotype) |
| **Statistical Considerations** | While there is no statistical basis for the sample size, it has been selected based on prior experience with generation 2 ASOs given by IT bolus injection to ensure that the safety, tolerability, PK, and exploratory pharmacodynamics will be adequately assessed while minimizing unnecessary patient exposure.<br>**Multiple Ascending Dose, Part 1**<br>Placebo-treated patients will be pooled for analysis. The safety and tolerability of ISIS 814907 will be assessed by determining the incidence, severity, and dose-relationship of AEs and changes in laboratory parameters and other safety measures by dose. Safety results in patients dosed with ISIS 814907 will be compared with those from patients dosed with placebo. If CSF total tau protein level is reflective of target engagement, exploratory analyses will be conducted to characterize the relationship between dose, CSF PK, and reduction from baseline in CSF total tau protein level. Analyses of biomarker and clinical evaluations will include dose- and PK-dependent effects and comparisons between patients receiving ISIS 814907 and those receiving placebo. The impact of reported genetic modifiers of disease phenotype on study endpoints may be investigated.<br>**Long-Term Extension, Part 2**<br>Longer-term safety and tolerability of ISIS 814907 will be assessed by determining the incidence, severity, and dose-relationship over time of AEs and changes in laboratory parameters and other safety measures by dose and CSF PK. Exploratory analyses will be conducted to characterize the relationship between dose, CSF PK, and reduction from baseline in CSF total tau protein level over time. Analyses of biomarker and clinical evaluations will include dose- and PK-dependent effects and comparisons between patients receiving ISIS 814907 in both Parts 1 and 2 of the study, and those receiving placebo in Part 1 followed by ISIS 814907 in Part 2. |
| **Sponsor** | Ionis Pharmaceuticals, Inc. |

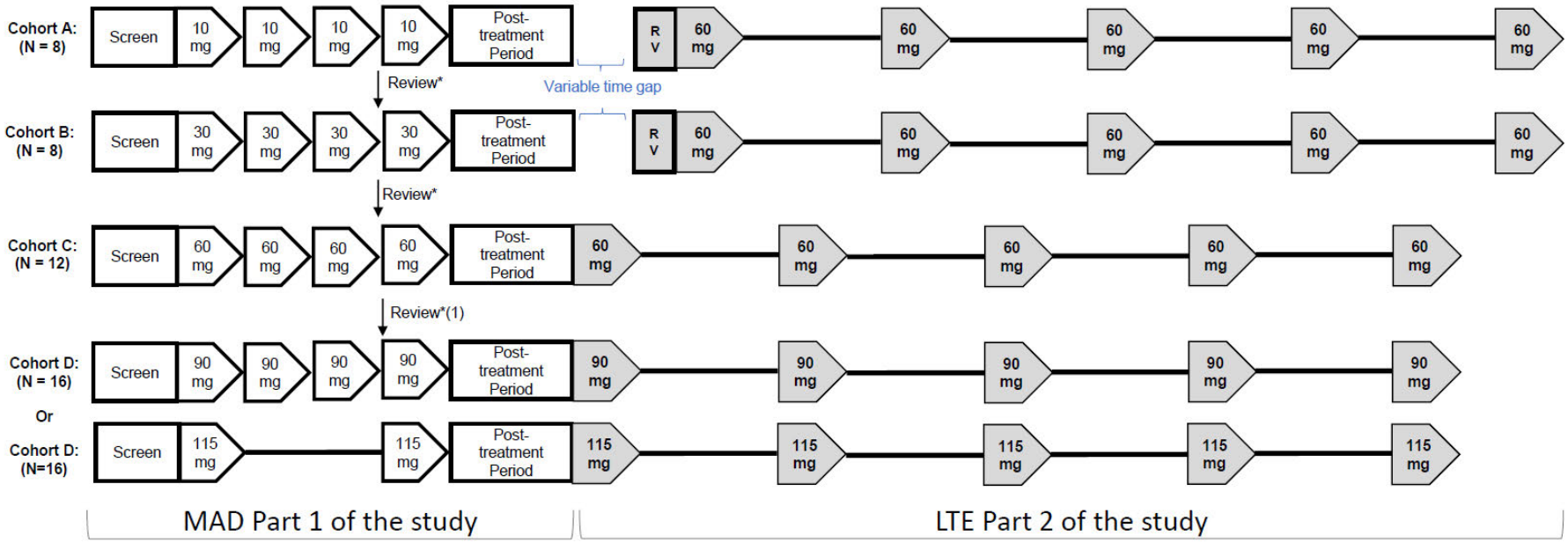
## STUDY DESIGN AND TREATMENT SCHEMA FOR MAD, PART 1



## STUDY DESIGN AND TREATMENT SCHEMA FOR LTE, PART 2



## COHORT ENROLLMENT FLOWCHART




The Multiple Ascending Dose, Part 1, of the study is represented by white boxes; the Long-Term Extension, Part 2, of the study is represented by grey boxes.

Note: Each pentagon represents 1 dose; in the MAD, Part 1, all doses are separated by a 28-day interval, or an 84-day interval for Cohort D (115 mg scenario). In LTE, Part 2, all doses in all Cohorts are separated by an 84-day interval.

Note: The first 2 patients at each dose level will be randomized 1:1 active:placebo and at least 1 week must elapse between dosing in these 2 patients and dosing in any other patients at this dose level.

*, FSMG (unblinded) and Sponsor (blinded) review of data to permit initiation of dosing in a new cohort will occur when at least 2/3 of the patients in the lower-dose cohort have been followed for at least 7 days after receipt of the last dose of Study Drug and all data that are required for the review through that timepoint are available.

Prior to dosing being initiated in a new cohort in the MAD, Part 1 of the study, the FSMG will review the safety, PK and PD data described above (at minimum) and make a recommendation regarding initiation of dosing in the new cohort. Dosing in a new cohort will not begin until enrollment in the prior cohort is complete. Additionally, PK and PD data will be compared to the ISIS 814907 levels and PD effects that are expected according to the preclinical PK/PD model. Based on this review, the dose level(s) for future cohort(s) may be adjusted. The maximum dose increment is as follows: from Cohort A to Cohort B, the increment can be no more than 3x; for all subsequent escalations, the increment from the current cohort to the next dose cannot be more than 2x the current dose level. The maximum dose level tested in a cohort will not exceed 115 mg. In the MAD, Part 1, the dosing regimen for Cohort D may be changed from 4 doses over 3 months to 2 doses over 3 months.

(1) Once the FSMG has reviewed the Cohort C data package for the dose-escalation meeting to Cohort D (2/3 of patients in Cohort C having received all doses of Study Drug in Part 1 with safety data up to 7 days post-last dose), the patients from Cohorts A and B will be invited back to start the LTE, Part 2 at the Cohort C dose. All dosing in Part 2 will be quarterly (e.g., 84-day dosing interval).

## STUDY GLOSSARY

| Abbreviation | Definition |
|---|---|
| 2′-MOE | 2′-*O*-(2-methoxyethyl) |
| AD | Alzheimer's disease |
| AE | Adverse event |
| ALT | Alanine aminotransferase (SGPT) |
| apoE 4 | Apolipoprotein E4 |
| APP | Amyloid precursor protein |
| aPTT | Activated partial thromboplastin time |
| ARWMC | Age-related white matter changes |
| ASL | Arterial spin labeling |
| AST | Aspartate aminotransferase (SGOT) |
| AUC | Area under the curve |
| $AUC_t$ | Area under the plasma concentration-time curve from time zero to time t |
| BCHE | Butyrylcholinesterase |
| BCHE-K | Butyrylcholinesterase K variant |
| BMI | Body Mass Index |
| BP | Blood pressure |
| BUN | Blood urea nitrogen |
| CDR | Clinical Dementia Rating |
| $C_{max}$ | Maximum concentration |
| cl | Clinic |
| CNS | Central Nervous System |
| CRF | Case report form |
| C-CSA | Columbia-Classification Algorithm for Suicide Assessment |
| CSF | Cerebrospinal fluid |
| C-SSRS | Columbia suicide severity rating scale |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLT | Dose-limiting toxicity |
| DTI | Diffusion Tensor imaging |
| ECG | Electrocardiogram |

**STUDY GLOSSARY *Continued***

| Abbreviation | Definition |
|---|---|
| eCRF | Electronic Case Report Form |
| FAQ | Functional Activities Questionnaire |
| FDG | Fluorodeoxyglucose |
| FH | Factor H |
| FSE | Fast spin echo |
| FSH | Follicle stimulating hormone |
| FSMG | Formal Safety Monitoring Group |
| FTLD | Frontotemporal lobar degeneration |
| FTLD-tau | Frontotemporal lobar degeneration with tau inclusions |
| GCP | Good Clinical Practice |
| HED | Human equivalent dose |
| HIV | Human Immunodeficiency Virus |
| HR | Heart rate |
| ICH | International Conference on Harmonization |
| ICV | Intra-cerebral ventricular |
| IEC | Independent Ethics Committee |
| IL-1β | Interleukin-1 beta |
| IL-6 | Interleukin-6 |
| INR | International normalized ratio |
| IRB | Institutional Review Board |
| ISIS 814907 | Antisense inhibitor of *MAPT* |
| IT | Intrathecal(ly) |
| IUD | Intrauterine contraceptive device |
| LLN | Lower limit of normal |
| LP | Lumbar puncture |
| LTE | Long-term extension |
| MAD | Multiple ascending dose |
| MCH | Mean corpuscular hemoglobin |
| MCHC | Mean corpuscular hemoglobin concentration |
| MCI | Mild cognitive impairment |

**STUDY GLOSSARY *Continued***

| Abbreviation | Definition |
|---|---|
| MCP-1 | Monocyte chemoattractant protein-1 |
| MCV | Mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMSE | Mini-mental state examination |
| MRI | Magnetic resonance imaging |
| mRNA | Messenger ribonucleic acid |
| MTD | Maximum tolerated dose |
| NCS | Not clinically significant |
| NfL | Neurofilament light chain |
| NFT | Neurofibrillary tangle(s) |
| NIA-AA | National Institute of Aging-Alzheimer Association |
| NMDA | N-methyl-D-aspartate |
| NPI | Neuropsychiatric Inventory |
| NPI-Q | NPI Questionnaire |
| on Study | The patient is 'on Study' from signing of the informed consent until his/her last study visit |
| PET | Positron emission tomography |
| pH | Measure of the acidity or basicity of a solution |
| PD | Pharmacodynamic(s) |
| PK | Pharmacokinetic(s) |
| PT | Prothrombin time |
| RBANS | Repeatable Battery for the Assessment of Neuropsychological Status |
| RNase H1 | An ubiquitous endonuclease that specifically hydrolyzes the RNA strand in RNA/DNA hybrids |
| S100B | S100 calcium binding protein B |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SBP | Systolic blood pressure |
| SNAP25 | Synaptosomal-associated protein 25 |
| SNP | Single nucleotide polymorphism |
| Study Drug | ISIS 814907 or placebo |

**STUDY GLOSSARY *Continued***

| **Abbreviation** | **Definition** |
|---|---|
| SUSAR | Suspected unexpected serious adverse reaction |
| TEAE | Treatment-emergent adverse event |
| $T_{max}$ | Time to maximal concentration |
| TNFα | Tumor necrosis factor alpha |
| TSE | Turbo spin echo |
| VILIP1 | Visinin-like protein 1 |
| WBC | White blood cell |
| WMH | White matter hyperintensity |
| YKL-40 | Chitinase-3-like protein 1 |

# 1. OBJECTIVES

## 1.1 Primary Objectives

To evaluate the safety and tolerability of ascending dose-levels of multiple intrathecal (IT) bolus administrations of ISIS 814907, an antisense inhibitor of *MAPT* messenger ribonucleic acid (mRNA) that encodes the tau protein, in patients with AD pathology.

## 1.2 Secondary Objectives

To characterize the cerebrospinal fluid (CSF) pharmacokinetics (PK) of ascending dose-levels of multiple IT bolus administrations of ISIS 814907.

## 1.3 Exploratory Objectives

To explore effects of multiple doses of ISIS 814907 on potential target engagement and disease progression biomarkers and clinical endpoints relevant to AD. Plasma PK properties of ISIS 814907 will also be assessed. Disease progression markers are included primarily as a safety measure to document any marked worsening. A lesser objective is to gain experience with these measures in an ISIS 814907 clinical study as preparation for subsequent, longer-term clinical studies. CSF total tau is a key exploratory endpoint. If CSF total tau protein level is reflective of target engagement, exploratory analyses will be conducted to characterize the relationship between dose, CSF PK, and CSF tau protein level. It is not expected that the majority of biomarkers and clinical measures will be impacted significantly by the 3 months of ISIS 814907 administration planned for Part 1; however, the longer-term treatment with ISIS 814907 in Part 2 may affect both biomarkers and clinical measures.

# 2. BACKGROUND AND RATIONALE

## 2.1 Overview of Disease

### *2.1.1 Tau Protein and Alzheimer's Disease*

ISIS 814907 is in development for the treatment of tauopathies, which include frontotemporal lobar degeneration (FTLD) and Alzheimer's disease (AD).

The microtubule-associated protein tau has a natively unfolded, highly soluble structure (Goedert and Spillantini 2006). Tau protein is subject to a complex array of tightly regulated post-translational modifications, including phosphorylation (Morris et al. 2011b). Altered post-translational modification, such as hyperphosphorylation, result in tau losing the ability to interact with microtubules, becoming more susceptible to filament formation, and aggregating into inclusions called neurofibrillary tangles (NFTs) (Goedert et al. 1989; Bramblett et al. 1993; Yoshida and Ihara 1993; Alonso et al. 1994; Lee et al. 2001). Neurofibrillary tangles are associated with synaptic and neuronal loss.

Pathogenic accumulations of tau appear to traverse through the brain along neuronally connected pathways to the hippocampus and ultimately the neocortex (Braak and Del Tredici 2011; Hyman 2014). Misfolded protein aggregates "spread" through the brain, corrupting naïve tau monomers as they propagate. Aggregation of tau into NFTs appears to be the primary pathology in some disorders, including frontotemporal lobar degeneration with tau inclusions (FTLD-tau) (Morris et

al. 2011b; Onyike and Diehl-Schmid 2013). In other neurodegenerative diseases such as AD, tau is not the initiating pathology but appears to be a key secondary effector of the disease process. In AD - unlike amyloid deposits that appear diffusely throughout the brain - tau deposits seem to map closely to regions where atrophy occurs and cognitive deficits originate. This supports tau as a therapeutic target, particularly in the symptomatic phase of AD.

### *2.1.2 Epidemiology, Clinical Features and Diagnosis*

This study will enroll patients with mild AD.

AD is the most common type of dementia. The age-specific prevalence of AD almost doubles every 5 years after age 65. Among developed nations, approximately 1 in 10 people 65 years or older is affected by some degree of dementia (von Strauss et al. 1999; Corrada et al. 2008). A proportion of these cases involve solely Alzheimer's pathology, while the remainder evidence concomitant pathologies related to other dementias and age-related changes. The latter group is sometimes called mixed dementia and is more common over the age of 75 years.

AD is a slowly progressive brain disease beginning well before clinical symptoms emerge. It can be categorized into 3 stages: (i) preclinical AD, (ii) mild cognitive impairment (MCI) due to AD, and (iii) dementia due to AD (Albert et al. 2011; Jack et al. 2011; McKhann et al. 2011); (Sperling et al. 2011). The brain changes of AD may begin 20 or more years before symptoms appear (Villemagne et al. 2013), and individuals progress through the disease at different rates (Lane and He 2009). With the earliest brain changes, individuals are usually able to function normally. Later, when the brain can no longer compensate for the neuronal damage that has occurred, a subtle decline in cognitive function emerges. With further deterioration, the damage to and death of neurons becomes so significant that the cognitive decline is obvious, generally characterized by memory loss or confusion as to time or place. Significant functional impairment associates with the transition to a dementia diagnosis. Eventually, basic bodily functions, such as swallowing, become impaired.

The hallmark pathologies of Alzheimer's disease are progressive accumulation of Aβ into plaques outside neurons in the brain and NFTs inside neurons. These changes are eventually accompanied by aberrant network activity, excitotoxicity, dysfunction and loss of synapses, shrinkage and loss of neurites, and death of neurons (Huang and Mucke 2012).

Although Aβ accumulation and plaque deposition are thought to be the initiating events in Alzheimer's disease (AD) development, tau pathology correlates better than Aβ pathology with cognitive impairment (Arriagada et al. 1992). Tau inclusions appear before Aβ deposition in most people as they age (Braak and Braak 1997), but AD arises only when Aβ deposition coexists (Price et al. 2009; Fortea et al. 2014). Tau is necessary for Aβ-induced neurotoxicity (Ittner and Gotz 2011), but Aβ drives tau pathology, not the reverse (Spillantini and Goedert 2013). Thus, Aβ appears to act upstream of tau, and it is believed that its adverse effects are mediated by tau (Huang and Mucke 2012).

### *2.1.3 Treatments for Mild AD*

Due to the lack of therapies that can delay the onset or slow the progression of AD in patients, the current goals of treatment are aimed at reducing the burden of symptoms, maximizing

function and optimizing the patient's quality of life. Symptomatic treatment options are tailored to the individual patient's symptoms and stage of disease progression.

Drugs currently approved by the FDA for the treatment of dementia due to AD inhibit acetylcholinesterase to increase the levels of the neurotransmitter acetylcholine or antagonize N-methyl-D-aspartate (NMDA)-type glutamate receptors (Cummings 2004). The impact of these drugs on disease manifestations is modest, benefit appears to be transient and there is no convincing evidence that these agents can modify the pathological processes underlying the disease.

## 2.2 Therapeutic Rationale

Decreasing the production of the tau protein is expected to be beneficial in tauopathies due to a tau protein *toxic gain-of-function* (caused by misfolded oligomeric or protofibrillar NFT precursor species, mislocalized tau or a direct neurotoxic effect of NFTs) (Morris et al. 2011b; Spillantini and Goedert 2013). As the pathologic species of tau are not well-understood, it may be desirable to reduce all forms of tau to prevent the formation of all toxic species in all compartments.

An advantage of tau knockout (*Tau*$^{-/-}$) models is that they can show if tau has unique functions that are not redundant with the functions of other proteins. Genetic ablation of total endogenous Tau$^{-/-}$ in 4 mouse lines results in viable, fertile mice with no grossly observable phenotype 3 (Harada et al. 1994; Dawson et al. 2001; Tucker et al. 2001; Fujio et al. 2007; Roberson et al. 2007; Muramatsu et al. 2008; Dawson et al. 2010; Ittner et al. 2010; Roberson et al. 2011). These knockout mice have normal motor learning and memory, motor function, anxiety levels, and exploration. One fairly consistent abnormality in *Tau*$^{-/-}$ mice is mild motor deficits generally reflecting hyperactivity (Morris et al. 2013; Ikegami et al. 2000). The finding that these Tau$^{-/-}$ mice develop normally suggests that other proteins, such as MAP1B, can substitute for tau in stabilizing microtubules and its other functions, at least in most circumstances (Ke et al. 2012; Morris et al. 2013; Lei et al. 2014). Reduced levels of tau do not appear to result in a loss of normal functions, such as a loss of microtubule stabilization and axonal transport (King et al. 2006; Qiang et al. 2006; Yuan et al. 2008; Vossel et al. 2010). These data suggest that neuropathological abnormalities in tauopathies are due to a *toxic gain-of-function* of tau and not a *loss of normal function*.

However, accumulating evidence suggests a role for tau in the regulation of synaptic function and neuronal signaling (Pooler et al. 2014). *Tau*$^{-/-}$ mice display compromised synaptic function, evidenced by impaired long-term potentiation (LTP) at 6 (Ahmed et al. 2014), and 12 months of age (Kimura et al. 2014). Furthermore, a mild phenotype has been reported in some *Tau*$^{-/-}$ mouse lines. Of the studies conducted in younger mice (< 1 year), there is little evidence of any significant motor impairment (Harada et al. 1994; Ikegami et al. 2000; Morris et al. 2011a; Lopes et al. 2016; Lei et al. 2012; Li et al. 2014). Of the studies conducted in older mice ≥ 1 year, some have demonstrated mild motor impairment (Morris et al. 2013; Lei et al. 2012; Ma et al. 2014; Lopes et al. 2016), while others have no evidence of motor impairment (Li et al. 2014; Morris et al. 2013). When evidenced, the etiology of motor dysfunction has been controversial, with one Investigator attributing this to loss of dopaminergic neurons in the substantia nigra caused by iron accumulation in the brain (Lei et al. 2012; Lei et al. 2014), while others found no evidence for this pathology (Morris et al. 2013; Li et al. 2014). Yet another Investigator

attributes motor dysfunction to a peripheral nervous system etiology exemplified by degenerating fibers and hypomyelination of large-diameter, motor-related fibers and diminished conduction properties in old, but not young, *Tau*$^{-/-}$ sciatic nerve (Lopes et al. 2016). Of the studies conducted in older mice ≥ 1-year, some have demonstrated cognitive impairment (Ma et al. 2014; Lei et al. 2012), but others have not (Li et al. 2014; Morris et al. 2013). Results suggest that genetic background may impact the phenotype in *Tau*$^{-/-}$ mice (Lei et al. 2014).

As the aforementioned studies utilized conventional knockout models (where tau is deficient from birth) rather than conditional knockout models, it is not possible to determine from these studies whether chronic and substantial reduction, but not complete elimination, of *MAPT* mRNA and tau protein commencing in adulthood will have any effects on phenotype. Studies with heterozygous knockout models (*Tau*$^{+/-}$) can be used to investigate the effects of partial tau elimination (from birth). Partial loss of tau in *Tau*$^{+/-}$ mice has not been associated with significant abnormalities in any study, even with aging, suggesting that loss-of-function plays little, if any, role in the phenotypic deficits in tauopathies (Lei et al. 2012; Lei et al. 2014; Morris et al. 2013). The complete lack of any phenotype in the *Tau*$^{+/-}$ mice indicates that down-regulation of tau gene expression by 50% should not pose a safety concern. Similarly, a lack of an overt phenotype in most *Tau*$^{-/-}$ mouse models suggests that a complete ablation of tau gene expression in adult life after the completion of neurodevelopment should not pose a safety concern. However, this outcome is less certain, and some results suggest caution against excessive lowering of CNS tau (Lei et al. 2012; Lei et al. 2014). Administration of ISIS 814907 in animals leads to dose-dependent reduction of *MAPT* mRNA and tau protein. Complete elimination of *MAPT* mRNA and tau protein is not achievable and pharmacological effects are reversible following discontinuation of ISIS 814907 administration.

*Antisense targeting of MAPT mRNA in mouse models of AD*

In AD patients tau is not mutated, yet NFTs form, and tau appears to contribute to the disease. Homozygous or hemizygous knockout of endogenous tau expression suppress Aβ-induced behavioral deficits in a transgenic mouse model of AD (Roberson et al. 2007; Ittner et al. 2010; Vossel et al. 2010; Leroy et al. 2012) and confirms a critical role for tau in transducing Aβ-linked neurotoxicity. Lowering endogenous levels of murine tau using the tau knockout line has proven protective against a growing number of Aβ-induced insults, including cognition (Roberson et al. 2007; Ittner et al. 2010; Andrews-Zwilling et al. 2010; Leroy et al. 2012), hyperexcitability (Roberson et al. 2007; Ittner et al. 2010; Suberbielle et al. 2013; Li et al. 2014), hippocampal long-term potentiation (Shipton et al. 2011), axonal transport defects (Vossel et al. 2010), survival (Roberson et al. 2007; Ittner et al. 2010), cell-cycle re-entry (Seward et al. 2013), double stranded breaks in DNA (Suberbielle et al. 2013), and neuroinflammation (Maphis et al. 2015). Two (2) independent mechanisms may contribute to the benefits of tau suppression in AD: firstly, the prevention and reversal of tau aggregation and of tau spreading and, secondly, the prevention of Aβ-induced hyperexcitability.

Moreover, an ASO selectively decreased human *MAPT* (h*MAPT*) mRNA by ~50% and tau protein expression throughout the brains of adult Tau$^{P301S}$ tauopathy mice when administered ICV for 1 month before, at the onset, and post-pathology development (DeVos et al. 2017):

- *Tau inclusions* were substantially reduced after a further 2 months of follow-up

- *Pre-existing hyperphosphorylated tau, ThioS pathology and accompanying astrogliosis* were reversed in older animals with pre-existing tau deposits
- Further *hippocampal volume loss* and CA1 neuronal death was prevented in aged $Tau^{P301S}$ mice
- The *seeding potential of misfolded tau* corrupting naïve tau to induce further aggregation was apparently reduced in tissues from $Tau^{P301S}$ mice treated with hTau lowering ASOs

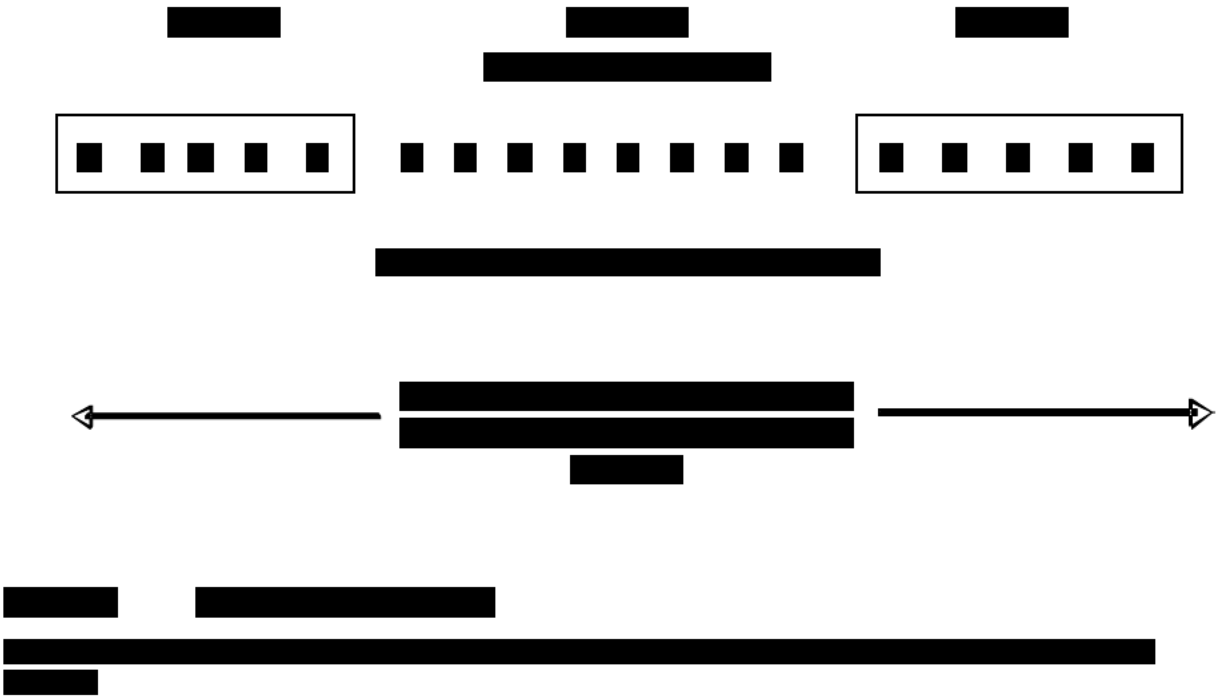
Direct intra-cerebral ventricular (ICV) administration dose-response study of an ASO targeting *MAPT* mRNA in 2 chemically induced seizure mouse models (DeVos et al. 2013) showed substantial downregulation of *MAPT* mRNA and reduction of a *tau-associated seizure* phenotype. Importantly no adverse behavioral effects were observed (DeVos et al. 2013); (DeVos et al. 2017).

Thus, preclinical models suggest that ISIS 814907 is a promising approach to reduce tau safely and to a therapeutically relevant degree (see Section 2.3.3). These data also support the use of a tau-lowering therapy in patients after pathological tau deposition in the brain has already begun.

The known potential risks associated with ISIS 814907 as well as study-associated risks, such as risks related to the lumbar puncture (LP), are described on in the Guidance to Investigator section of the Investigator's Brochure.

## 2.3 ISIS 814907

[redacted]



### *2.3.3 Preclinical Experience*

Detailed information concerning the preclinical studies conducted with ISIS 814907 can be found in the Investigator's Brochure. A summary is included below.

Preclinical proof-of-concept studies with ASOs targeting *MAPT* mRNA have been conducted in the P301S mouse model of FTLD, a mouse strain expressing human *MAPT* with the P301S FTLD mutation that develops tau pathology at 4-6 months of age, including accumulations of hyperphosphorylated tau and NFTs. Also, misfolded tau in brain lysate from P301S mice is able to seed tau aggregates when injected into brains of other animals (i.e., induce further misfolding and accumulation of tau protein), mimicking a proposed mechanism for tauopathy pathology. In these studies, ASOs targeting human *MAPT* mRNA not only prevented pathological changes but also reversed existing pathology, clearing pre-existing neuronal tau accumulations and reducing the seeding ability that likely contributes to spread of further pathology.

Additional proof-of-concept studies have been conducted to explore the potential benefits of tau suppression in AD, in which pathological NFTs form and contribute to disease despite there being no mutation in tau. An emerging hypothesis for the contribution of tau to Aβ toxicity is that tau contributes to amyloid precursor protein (APP)-induced aberrant hyperexcitability. To test for a relationship between tau and hyperexcitability, adult wild-type mice were treated with a mouse *MAPT* ASO and subjected to chemically induced hyperexcitability. A correlation was observed between tau protein level and neuronal hyperexcitability, supporting the hypothesis that normal (i.e., non-mutant) tau contributes to hyperexcitability.

The PK and toxicity of ISIS 814907 were assessed following 13 weeks of repeated IT lumbar bolus injections (4 to 35 mg bi-weekly for the first month (Days 1, 14, and 28) followed by

monthly injections on Days 56 and 84) in cynomolgus monkeys. Potential systemic toxicity of ISIS 814907 was also evaluated following 13 weeks of repeated subcutaneous administration (once weekly) in mice. Detailed results from these preclinical studies conducted with ISIS 814907 can be found in the ISIS 814907 Investigator's Brochure.

### *2.3.4 Clinical Experience*

ISIS 814907 has not been evaluated in any clinical setting.

## 2.4 Rationale for Study Design

### *2.4.1 Rationale for the Study Population*

This is the first study of ISIS 814907 in humans, and it will be conducted in patients with mild AD. It is necessary to conduct this study in patients, rather than in healthy volunteers, because ISIS 814907 is a CNS-acting agent to be administered via IT administration and consideration of the balance between risk and benefit justifies investigation in a patient population only. Although the assessment of safety is the primary objective of this study, the patients in the study may not be too advanced in their disease process to enable detection of clinical and/or biomarker changes that are reflective of target engagement and downstream pharmacodynamics (PD) responses, suggesting potential for clinical benefit to be demonstrated.

In this study, patients are aged ≥ 50 years and ≤ 74 years to avoid undesirable comorbid illness that is more common in older individuals. Moreover, in older, late-onset AD patients, Alzheimer's pathology is usually confounded by multiple, non-AD, age-related neurodegenerative pathologies.

### *2.4.2 Rationale for a Multiple Ascending Dose Design*

This is a first-in-human, multiple ascending dose (MAD; Part 1) and long-term extension (LTE; Part 2) study in patients with mild AD.

Part 1 of the study is designed to capture the information that traditionally might be obtained in 2 separate studies – a single ascending dose study and a MAD study. The inter-dose interval makes this design feasible: Under the 4-dose regimen, Study Drug dosing occurs at 28-day intervals and allows for comprehensive safety and tolerability evaluations to be conducted in each patient for 28 days after the first dose. At the conclusion of the first 28-day period, once monthly (28-day interval) dosing will continue for 3 additional doses, allowing for evaluation of safety, tolerability, PK, and target engagement during a multiple-dose regimen. Under the 2-dose regimen, that may be implemented in Cohort D only, Study Drug dosing occurs at an 84-day interval, allowing for comprehensive safety and tolerability evaluations to be conducted in each patient for 84 days after the first dose. Under this 2-dose regimen, the Study Drug will only be given twice in 3 months.

Preclinical efforts have identified the ISIS 814907 brain tissue concentrations that are predicted to be necessary for clinical benefit. If toxicities are related to maximum concentration ($C_{max}$), these concentrations are more safely approached through multiple (lower) dose administration than through single, high-dose administration.

Patient safety is also the motivation behind other elements of the study criteria. For example, only Study Centers with clinical research facilities with capabilities for 24-hour in-patient monitoring will be utilized, patients must remain in the Study Centers overnight or for an extended observation after each dose of Study Drug and patients will be required to live close enough to the facility to permit prompt appearance at the facility if requested. Each patient will be required to have a trial partner (i.e., a reliable and competent individual with a close relationship with the patient), and the Investigator will seek supplemental information about the patient's condition from the trial partner using validated tools. In addition, patient safety will be monitored closely during the study by an unblinded Formal Safety Monitoring Group (FSMG), which will have access to all study data, including PK and PD data. As an additional safety measure in the LTE, Part 2, of the study all patients must be kept at the Study Center for at least 24 hours following the first ISIS 814907 administration and undergo safety monitoring as scheduled. This 24-hour safety monitoring is required as it will not be known which patients received placebo in Part 1 and are therefore receiving ISIS 814907 for the first time in Part 2. For all subsequent administrations of ISIS 814907 in Part 2, the inpatient post-dose assessments may be reduced to a minimum of 6 hours.

### *2.4.3 Rationale for Dose Levels and Dosing Schedule*

The proposed study will test the safety, tolerability, and PK of multiple doses of ISIS 814907 administered as IT bolus injections. Four (4) dose levels will be evaluated. The doses selected are predicted to produce a range of pharmacologic effect but are not intended to elicit dose-limiting toxicities (DLT). [redacted]

In monkey toxicology studies, the NOAEL was determined to be 35 mg. Conservatively correcting for differences in CSF volume between monkey (≤ 15 mL) and humans (≥ 150 mL) with a scaling factor of 10, the putative human NOAEL dose is equivalent to a dose level of 350 mg/dose (1750 mg total dose over the 3-month dosing period). The lowest planned dose level of 10 mg (40 mg cumulative over 3 months) is 35-fold (44-fold cumulative) lower than the NOAEL of 350 mg (1750 mg cumulative over 3 months). A dose level of 90 mg (360 mg cumulative over 3 months) is 3.8-fold (4.8-fold cumulative) lower than the NOAEL established in preclinical toxicology program. The highest planned dose level of 115 mg given twice over 3 months (230 mg cumulative over 3 months) is 3-fold (7-fold cumulative) lower than the NOAEL established in preclinical toxicology program. [redacted]

[redacted] Also, monthly dosing is expected to be safe and well-tolerated by patients. The collected PK and PD data from each cohort will be analyzed to better understand the half-life of the drug and its accumulation as well as the half-life of the tau protein in the human CSF and its reduction; if the Study Drug exhibits better PD effect and/or more drug accumulation than anticipated, it may be possible to assess quarterly (84-day interval) dosing instead of monthly (28-day interval) dosing in Part 1, as this would benefit the patients by reducing the number of lumbar punctures. The FSMG will have the responsibility to review the PK and PD data and recommend the adjustment of the dosing interval from 4 doses of Study Drug over 3 months to 2 doses of Study Drug over 3 months in Part 1 of the study.

The aim of Part 2 is to evaluate the safety, PK and PD effects of a quarterly (84-day) dose interval of 2 dose levels of ISIS 814907. Cohort C patients will seamlessly transition to LTE Part 2 after completing Part 1, and they will continue the Cohort C dose with a quarterly (84-day) dose interval in the LTE, Part 2. Cohort D patients will also seamlessly transition to LTE, Part 2 after completing Part 1, and they will continue the Cohort D dose with a quarterly (84-day) dose interval in the LTE, Part 2. Cohort A and B patients who have completed the Treatment Evaluation and Post-Treatment Periods in Part 1 are also eligible to enter LTE, Part 2 of the study. They will start LTE, Part 2 at the Cohort C dose with a quarterly (84-day) dose interval, if permitted by the FSMG review of the Cohort C package for the dose-escalation meeting to Cohort D (2/3 of patients in Cohort C having received all doses of Study Drug in Part 1). It is anticipated that patients entering the LTE, Part 2 will be maintained on the dose they received when they initiated Part 2. However, dose levels and dosing regimen in the LTE could be adjusted in individuals or for the entire study based on ongoing review of the safety, PK/PD profile by the FSMG and the Sponsor. Depending on safety and PK/PD data emerging from the entire study, including the LTE, the FSMG and Sponsor may decide to adjust the Part 2 dose and/or dosing regimen in some or all patients to a new dose level that is thought likely to be an optimal therapeutic dose level and that does not exceed a dose of 115 mg.

Additional details on dose scaling and expected CSF and tissue concentrations are summarized in the Investigator's Brochure.

## 3. EXPERIMENTAL PLAN

### 3.1 Study Design

This is a Phase 1, multi-center, double-blind, randomized, placebo-controlled study of multiple IT bolus administrations of ISIS 814907 in patients with mild AD aged 50-74 years.

This study is divided into 2 parts:

- Part 1: a randomized, double-blind, placebo-controlled multiple ascending dose (MAD) part, comprising a Screening Period of 8 weeks, a Treatment Evaluation Period of 13 weeks, and a Post-Treatment Period of 23 weeks
- Part 2: an open-label, long-term extension (LTE) part, comprising a Registration Period of 3 weeks (only for those who cannot transition seamlessly, i.e., patients from Cohorts A and B), a Treatment Evaluation Period of 48 weeks, and a Post-Treatment Period of 16 weeks
    - For patients participating in Cohorts A and B there will be a variable gap of time between the end of Part 1 and entry into Part 2
    - Patients participating in Cohorts C and D will seamlessly transition from Part 1 to Part 2. Day 253 in Part 1 will correspond to Day -1 in Part 2.

### *3.1.1 Multiple Ascending Dose, Part 1*

Four (4) ascending dose level cohorts (A, B, C, and D) of patients will be enrolled sequentially and randomized with an overall ratio of 3:1 to receive ISIS 814907 or placebo. A sentinel dosing strategy will be implemented. The first 2 patients at a given dose level will be assigned 1:1 active:placebo, and at least 1 week must elapse between initiation of treatment in these 2 patients and initiation of treatment in additional patients at this dose level. The remaining patients will be assigned to active or placebo at a 5:1 ratio (cohorts with N = 8), 8:2 ratio (cohorts with N = 12), or 11:3 ratio (cohorts with N = 16) to ensure a 3:1 active:placebo balance in the cohort. Based on the profile of effects observed in non-human primate toxicology studies, 24 hours is expected to be a sufficiently long observation period to identify possible safety issues. As a safety measure, the sentinel dosing algorithm utilized for this study will require that 1-week elapses between initiation of treatment in the first 2 patients and initiation of treatment in subsequent patients in the cohort. Identified and potential risks associated with ISIS 814907 are described in detail in the Investigator's Brochure.

Initiation of dosing in a new cohort may begin after 3 conditions have been met: (1) all patients in the lower-dose cohorts have been enrolled, (2) at least 2/3 of the patients in the lower-dose cohort have been followed for at least 7 days after receipt of the fourth dose of Study Drug, and (3) a review of data (safety, PK, and PD data) collected in the lower-dose cohorts has been conducted by the FSMG and a decision has been made to proceed with the next cohort (see Section 3.7).

A communication plan will be created and used to ensure adequate communication between the Sponsor and study centers. The plan will mandate frequent interactions and timely dissemination of study updates, particularly as related to patient enrollment, dose escalation and safety data. Additionally, patient enrollment will be constrained by an electronic system (an interactive voice/web response system, IXRS). The IXRS permits enrollment at a single dose level at a given time, with the dose level defined by the Sponsor. The IXRS can be used to manage sentinel dosing, and it actively ensures that no site "escalates" prematurely, i.e., enrolls a patient in a higher-dose cohort before the FSMG and Sponsor have had the opportunity to conduct the protocol-specified dose escalation algorithm.

Each patient will receive 4 doses of Study Drug with a 28-day interval between doses. In the event of a dosing interval change, each patient will receive 2 doses of Study Drug with an 84-day interval between doses. The doses planned for the study are shown below. Based on emerging safety data from this study, one or more cohorts may be expanded by enrolling additional patients. Additionally, PK and PD measures will be collected at each dose level and compared to the results that are predicted by models constructed from preclinical data. The doses utilized in remaining cohorts may be adjusted, and/or additional cohorts of patients may be added, if necessary to achieve pharmacologically relevant levels. The maximum dose increment is as follows: from Cohort A to Cohort B, the increment can be no more than 3x; for all subsequent escalations, the increment from the current cohort to the next cannot be more than 2x the current dose level. The maximum dose tested in a cohort will not exceed 115 mg.

Cohort A: N = 8, mild AD, 10 mg ISIS 814907 or placebo x 4 doses

Cohort B: N = 8, mild AD, 30 mg ISIS 814907 or placebo x 4 doses

Cohort C: N = 12, mild AD, 60 mg ISIS 814907 or placebo x 4 doses

Cohort D: N = 16, mild AD, 90 mg ISIS 814907 or placebo x 4 doses *or* 115 mg ISIS 814907 x 2 doses

The overall randomization ratio in each cohort is 3:1 ISIS 814907 to placebo.

Following the 3-month Treatment Evaluation Period, there will be a 6-month Post-Treatment Period.

### *3.1.2 Long-Term Extension, Part 2*

The open-label LTE, Part 2, of the study will start with Cohort C and allow all patients in Cohorts C and D to seamlessly transition from Part 1 to Part 2. This means that for Cohorts C and D patients Day 253 in Part 1 will correspond to Day -1 in Part 2. In Part 2, the Treatment Evaluation Period of 48 weeks will be followed by a Post-Treatment Period of 16 weeks.

All patients will receive ISIS 814907 in Part 2 and will be dosed at an 84-day interval, regardless of the dose interval utilized in Part 1. Cohort C patients will continue the Cohort C dose with a quarterly (84-day) dose interval in the LTE, Part 2; Cohort D patients will continue the Cohort D dose with a quarterly (84-day) dose interval in the LTE, Part 2. Cohort A and B patients who have completed the Treatment Evaluation and Post-Treatment Periods in Part 1 are also eligible to enter Part 2 of the study. For Cohorts A and B patients there will be a variable gap of time between the end of Part 1 and entry into Part 2. There is no prescribed minimum or maximum interval of time required before Cohort A and B patients completing Part 1 can enter Part 2 of the study, however all Cohort A and B patients participating in the LTE, Part 2, should be enrolled in Part 2 prior to the last patient in Cohort D entering Part 2 of the study. Patients who participated in Cohorts A and B will be able to start the LTE, Part 2 of the study at the Cohort C dose with a quarterly (84-day) dose interval, if permitted by the FSMG review of the Cohort C package for the dose-escalation meeting to Cohort D (2/3 of patients in Cohort C having received all doses of Study Drug in Part 1). Patients entering the LTE Part 2 will be maintained on the dose they received when they initiated Part 2. Dose levels and dosing regimen in the LTE, Part 2 could be adjusted in individuals or for the entire study based on ongoing review of the safety, PK/PD

profile by the FSMG and the Sponsor. In the LTE, Part 2, the Treatment Evaluation Period of 48 weeks will be followed by a Post-Treatment Period of 16 weeks.

Patients who prematurely discontinue the Treatment Evaluation Period in Part 2 should complete any follow-up visits associated with the most recent administration of ISIS 814907 (see Section 8.9) and should complete the Part 2 Post-Treatment Period.

## 3.2 Number of Study Centers

This study will be conducted at multiple centers worldwide.

## 3.3 Number of Patients

Approximately 44 patients are planned to be randomized in this study. The number of patients randomized may be higher if some patients need to be replaced, the sizes of the cohorts are expanded to obtain further experience with particular dose levels and/or additional cohorts are added. A maximum of 64 patients may be randomized.

## 3.4 Overall Study Duration and Follow-up

The overall study duration will vary depending on which cohort a patient participates in. Patients participating in Cohorts A and B, will complete Part 1, that consists of a Screening Period of up to 8 weeks, a 13-week Treatment Evaluation Period and a 23-week Post-Treatment Period; approximately 44 weeks (~10 months) in duration. Following a variable gap of time, Cohorts A and B patients who completed Part 1 of the study will be invited to participate in Part 2, that consists of a Registration Period of up to 3 weeks, a 48-week Treatment Evaluation Period and a 16-week Post-Treatment Period; approximately 67 weeks (~15 months) in duration. Patients participating in Cohorts C and D will complete Part 1 and seamlessly transition, without a gap, to Part 2 of the study at the Day 253 visit; thus, for patients in Cohorts C and D, the study will consist of approximately 44 weeks (~10 months) in Part 1 seamlessly followed by Part 2 consisting of approximately 67 weeks (~15 months). The total duration for Cohorts C and D patients will be approximately 111 weeks (~26 months). Please refer to the Schedule of Procedures in Appendix A for a detailed overview of both Parts 1 and 2 of the study.

### *3.4.1 Multiple Ascending Dose, Part 1*

Patient eligibility for the study will be determined within an 8-week Screening Period prior to patient entry into the Treatment Evaluation Period.

During the Part 1 Treatment Evaluation Period, eligible patients will report to the Study Center for monthly (28-day interval) or quarterly (84-day interval) administrations of Study Drug and for additional, non-dosing visits as described in the Schedule of Procedures in Appendix A.

Patients in Cohorts A and B will return to the Study Center for follow-up visits 4, 8, 12, and 24 weeks after the last dose of Study Drug during the Part 1 Post-Treatment Period. Patients in Cohorts A and B will have a final study visit in Part 1 as Study Day 253/Week 37 to complete Part 1; they will enter Part 2 of the study at a later time point. Patients in Cohorts C and D will return to the Study Center for follow-up visits 4, 8, 12, 16 and 24 weeks after the last dose of Study Drug during the Part 1 Post-Treatment Period. Patients in Cohorts C and D will transition seamlessly into Part 2 of the study with the Day 253 in Part 1 corresponding to Day -1 in Part 2.

### *3.4.2 Long-Term Extension, Part 2*

For patients in Cohorts C and D, patient eligibility has been determined at the start of Part 1. For patients from Cohorts A and B who are returning to Part 2, there will be a Registration Period during which eligibility will be confirmed. During the Part 2 Treatment Evaluation Period, all patients will report to the Study Center for quarterly (84-day interval) administrations of ISIS 814907 and for additional, non-dosing visits as described in the Schedule of Procedures in Appendix A. During the Part 2 Post-Treatment Period, all patients will return to the Study Center for follow-up visits 12 and 16 weeks after the last dose of ISIS 814907. The final study visit will be the Day 449/Week 64.

## 3.5 End-of-Study

Patients in Cohorts A and B will have 2 End-of-Study visits; one in Part 1 and one in Part 2. Patients in Cohorts C and D will have a single End-of-Study visit, the Part 2 End-of Study visit. The overall completion of the study is defined as last patient, last study visit in Part 2.

## 3.6 Formal Safety Monitoring Group

An unblinded FSMG will be assembled to review data collected on ISIS 814907 during this study. Based on its ongoing assessment of the safety and tolerability of ISIS 814907, the FSMG will provide recommendations to the study team for modifying, stopping or continuing the study as planned. The progression of the study from one cohort to the next will be determined by the study team and the FSMG, and this determination will generally be based on the number of DLTs observed in patients treated with ISIS 814907 as well as review of the PK and PD data collected in the study.

Details on the safety assessments, frequency of review, meeting schedules and controlled access to unblinded data will be outlined in the FSMG Charter. The FSMG will consist of at least 3 medical doctors, all experienced in the conduct of clinical studies in patients with neurodegenerative diseases and otherwise independent from the conduct of the study. The decisions of the FSMG will be recorded in minutes of the meeting.

## 3.7 Dose Escalation

Four (4) dose level cohorts (Cohorts A, B, C, and D) will be enrolled sequentially, with patients each receiving 4 doses of Study Drug at 28-day intervals, or 2 doses of Study Drug at an 84-day interval if a dosing interval change is implemented in Cohort D. The first 2 patients at a given dose level will be assigned 1:1 active:placebo, and at least 1 week must elapse between initiation of treatment in these 2 patients and initiation of treatment in additional patients at this dose level. The progression of the study from initiation of dosing in one cohort to the next will be determined by the Sponsor and the FSMG. When transitioning to a cohort with a new dose interval, the total dose of the 2-dose regimen (2 doses over 3 months) will not exceed the total dose of the previous 4-dose regimen cohort.

Beginning with Cohort B, dose administration in the cohort may commence only after the following minimum requirements are met in the prior cohort:

- All patients in the prior cohort have been enrolled

- At least 2/3 of the patients in the prior cohort have received all doses of Study Drug (ISIS 814907 or placebo), patient safety has been monitored for at least 7 days after receipt of the fourth dose and those data are available for review
- All available data (safety, PK and PD data) in the prior cohort have been reviewed by the FSMG, and the FSMG has recommended initiation of the new cohort

Additionally, the PK and PD data will be compared to the ISIS 814907 levels and PD effects that are expected according to the preclinical PK/PD model. This review will be conducted in a manner that does not associate individual data with particular patients for those involved in the conduct of the study. Based on this review, the dose level(s) and dosing interval for future cohort(s) may be adjusted and/or additional cohorts may be added. The maximum dose increment is as follows: from Cohort A to Cohort B, the increment can be no more than 3x; for all subsequent escalations, the increment from the current cohort to the next cannot be more than 2x the current dose level. The maximum single and cumulative doses administered in a cohort will not exceed 115 and 460 mg, respectively, which represent 3- and 4-fold safety margins below the human equivalent NOAEL established in non-human primates. So, a dose of 115 mg every quarter (84-day interval) represent 3- and 7-fold safety margins below the human equivalent single and cumulative NOAEL doses, respectively, established in non-human primates.

Operationally, patient enrollment will be constrained by an electronic IXRS. The IXRS permits enrollment at a single-dose level at a given time, with the dose level defined by the Sponsor. After the dose escalation algorithm described above is complete and the Sponsor and FSMG are in agreement that escalation is appropriate, the Sponsor will make the necessary selections within the IXRS to permit a patient to be enrolled in the higher-dose cohort. Prior to the Sponsor completing these selections in the IXRS, patients cannot be enrolled into higher-dose cohorts and Study Drug for higher-dose cohorts cannot be dispensed. This feature of the IXRS ensures that no site "escalates" prematurely, i.e., enrolls a patient in a higher-dose cohort before the FSMG and Sponsor have had the opportunity to conduct the protocol-specified dose escalation algorithm. In the MAD, Part 1 of the study, the IXRS system will also allow the flexibility to adjust the dosing interval from 4 doses of Study Drug over 3 months to 2 doses of Study Drug over 3 months, if the FSMG and the Sponsor deem it appropriate to assess quarterly (84-day interval) dosing instead of monthly (28-day interval) dosing (See Section 2.4.3). In the LTE, Part 2 of the study all patients will need to be entered into the IXRS system even if they transition seamlessly.

If a single DLT is encountered in a cohort, the cohort may be expanded by up to 100% to assess safety at that dose. If dosing in higher dose cohort(s) is ongoing at the time a single DLT is encountered in a lower dose cohort, further enrollment in the higher dose cohort(s) will stop until (1) all current patients have completed dosing and at least 7 days of post-treatment safety evaluations from the last dose and (2) the FSMG have reviewed these data. In addition, in the event of a single DLT, the FSMG will decide if further measures are required such as pausing or reducing dose in ongoing patients in the higher dose cohort(s). Enrollment in higher-dose cohorts will not resume until the FSMG has conducted these additional reviews.

If any of the following is observed in the study, dose escalation will not occur, and dosing will be terminated in the affected cohort and in any higher-dose cohorts that are ongoing.

- DLTs in 2 patients in a cohort
- One (1) SAE or 2 severe AEs in a cohort that are considered by the Investigator and Sponsor to be at least possibly related to Study Drug, with the exception of:
  - SAEs where the only seriousness criterion is hospitalization if the hospitalization was only for observation and no specific treatment was administered for the event leading to hospitalization
  - Events that are known (i) signs or symptoms of AD (with the exception of acute disease worsening that is inconsistent with the patient's prior disease course), (ii) effects of the LP injection procedure or (iii) effects of any other study procedure (e.g., venipuncture, magnetic resonance imaging [MRI] scan)

In these situations, the Sponsor and FSMG will determine if enrollment of additional patients at the previous (lower) tolerated dose or enrollment of a new cohort of patients at an alternative dose is required to consider a given dose to be the maximum tolerated dose (MTD).

*Adjustment of dose in the Long-Term Extension, Part 2*

Patients who were randomized to Cohort C in Part 1 will continue Part 2 at the Cohort C dose with a quarterly (84-day) dose interval; similarly, patients who were randomized to Cohort D in Part 1 will continue Part 2 at the Cohort D dose with a quarterly (84-day) dose interval. Cohort A and B patients will start Part 2 at the Cohort C dose with a quarterly (84-day) dose interval, if permitted by the FSMG review of the Cohort C data package for the dose-escalation meeting to Cohort D (2/3 of patients in Cohort C having received all doses of Study Drug in Part 1). Patients entering the Part 2 LTE will be maintained on the dose they received when they initiated Part 2. Depending on safety and PK/PD data emerging from the entire study, including the LTE, the FSMG and Sponsor may decide to adjust the Part 2 dose and/or dosing regimen in some or all patients to a new dose level and/or dose interval that is thought likely to be an optimal therapeutic dose regimen and that does not exceed a dose level of 115 mg.

## 3.8 Dose Limiting Toxicity

A suspected DLT is defined as an adverse event (AE) that, in the judgment of a Site Investigator, is of sufficient significance to be dose limiting, is possibly or definitely related to Study Drug (i.e., the AE is substantially less likely to occur in patients not administered the Study Drug) and that it is not a known: (i) sign or symptom of AD (with the exception of acute disease worsening that is inconsistent with the patient's prior disease course), (ii) effect of the LP injection procedure, or (iii) effect of any other study procedure (e.g., venipuncture, magnetic resonance imaging [MRI] scan).

At any timepoint throughout the study, if an Investigator considers an event to be a suspected DLT, the event will be referred to the unblinded FSMG (via the Ionis Medical Monitor) which will determine whether it constitutes a DLT. No further dosing may occur in any patient while the FSMG reviews the event.

If a suspected DLT occurs during IT injection of the Study Drug, administration of Study Drug to the patient must be stopped (i.e., the injection must be discontinued immediately); and, if the event is determined to be a DLT, no further Study Drug injections may be administered in this

patient. The Investigator must contact the Ionis Medical Monitor as soon as possible to discuss the case. The FSMG should determine (based on unblinded data review, if necessary) if any relevant findings have been observed in other patients in the study.

Patients who experience a DLT will discontinue study treatment but should complete any follow-up visits associated with the most recent dose (see Section 8.9) and should complete the Post-Treatment Period.

# 4. PATIENT ENROLLMENT

## 4.1 Screening

Before patients may be enrolled into the study, the Sponsor or designee requires a copy of the Study Center's written Independent Ethics Committee/Institutional Review Board (IEC/IRB) approval of the protocol, informed consent form, and all other patient information and/or recruitment material.

Patients must sign the consent form before any screening tests or assessments are performed. At the time of consent, the patient will be considered enrolled into the study and will be assigned a unique screening number before any study procedures, including screening procedures, are performed. At the time of randomization, patients will be assigned a unique patient identification number. This number will be used to identify the patient throughout the trial and must be used on all study documentation related to that patient. The screening number and patient identification number must remain constant throughout the entire study. In the event the patient is re-consented and re-screened, the patient must be given a new screening number. Screening numbers and patient identification numbers, once assigned, will not be re-used.

All patients in the study will keep the same patient identification number for both MAD, Part 1 and LTE, Part 2 of the study; whether they seamlessly transition to Part 2 (i.e., Cohort C and D patients) or whether there is a variable gap of time between the end of Part 1 and the start of Part 2 (i.e. Cohort A and B patients). Each patient will keep his/her original patient identification number assigned in Part 1.

## 4.2 Randomization

In the MAD, Part 1, of the study, a patient will be randomized after all Screening assessments have been completed and after the Investigator has verified that the patient is eligible per criteria in Section 5.1. No patient may begin treatment prior to randomization and assignment of a unique patient identification number.

Eligible patients will be randomized centrally by an automated system to receive ISIS 814907 or placebo. Within each cohort, randomization will be 3:1 ISIS 814907:placebo as outlined in Section 3.1.

The Sponsor or designee will prepare the randomization list.

In the LTE, Part 2, of the study, patients in Cohorts A and B will be registered after all Screening assessments for Part 2 have been completed and the Investigator has verified that the patient is eligible per criteria in Section 5.2. Patients in Cohort C and D will transition seamlessly based on the eligibility criteria in Section 5.1 and do not need to be reassessed prior to the start of

Part 2. In the LTE, Part 2, all eligible patients will be enrolled by an automated system to receive ISIS 814907. Patients will retain their patient identification number assigned in Part 1.

### 4.3 Replacement of Patients

Patients withdrawn early from the study who do not complete all scheduled doses of Study Drug (ISIS 814907 or placebo) in the MAD, Part 1, of the study and whose treatment assignment remains blinded may be replaced at the discretion of the Sponsor up to a limit of 25% of the cohort sample and only if the reason for premature discontinuation from the Treatment Evaluation Period does not involve a DLT. Replacement patients will be assigned to the same Study Drug (ISIS 814907 or placebo) as the patients who are being replaced without unblinding any study personnel. No more than 64 patients may be randomized. No patients will be replaced in the LTE, Part 2, of the study.

Patients whose randomization code has been broken will not be replaced.

### 4.4 Unblinding of Treatment Assignment

All patients, monitors and Study Center personnel related to the study will be blinded throughout the double-blind period of the study (MAD, Part 1). However, if a patient has suffered a Serious Adverse Event (SAE) (as defined in Section 9.3.3) and knowledge of the treatment assignment will impact the clinical management of the patient, the Investigator will have the ability to unblind the treatment assignment for that patient through an automated system. The Sponsor or designee will be informed of the unblinding of a patient within 24 hours. An unblinded randomization schema will be maintained securely at the Sponsor's (or designee's) Quality Assurance Department. In addition, all SUSARs will be unblinded by the Sponsor's or designee's Drug Safety and Quality Assurance personnel for the purpose of regulatory reporting (see Section 9.2).

Every reasonable attempt should be made to complete the early termination study procedures and observations (see Appendices A and B) prior to unblinding, as knowledge of the treatment arm could influence patient assessment.

In the MAD, Part 1, of the study all patients, monitors and Study Center personnel, including the site pharmacist, will be blinded to treatment assignment. The LTE, Part 2, of the study is open-label and all patients will receive ISIS 814907. Following the last patient, last visit in the MAD, Part 1 the ISIS 814907 study team will be unblinded to treatment assignment, however, treatment assignment from Part 1 will remain blinded to investigators and patients for the duration of the study (i.e., until the end of Part 2).

## 5. PATIENT ELIGIBILITY

To be eligible to participate in this study, candidates must meet the following eligibility criteria at the time point specified in the individual eligibility criterion listed.

## 5.1 Eligibility for Multiple Ascending Dose, Part 1

### *5.1.1 Inclusion Criteria for MAD, Part 1*

Patients must meet the following inclusion criteria to be eligible:

Target Population

1. Patient is able to read, understand, and provide written informed consent (signed and dated)
2. Male or female, aged 50-74 years, inclusive, at Screening
3. AD of mild severity (CDR Global score of 1 or CDR Global Score of 0.5 with a Memory score of 1; MMSE 20-27, inclusive) at Screening
4. Reduced CSF Aβ42 at Screening, consistent with a diagnosis of mild AD
5. Elevated CSF total tau and p-tau at Screening consistent with a diagnosis of mild AD
6. Diagnosis of probable AD dementia based on National Institute of Aging-Alzheimer Association (NIA-AA) criteria (may be either amnestic [Global CDR score of 0.5 or 1.0] or nonamnestic [Global CDR score of 1.0] presentation) at Screening
7. Body Mass Index (BMI) $\geq 18$ and $\leq 35$ kg/m$^2$
8. Total body weight > 50 kg (110 lbs)
9. Able and willing to meet all study requirements, including travel to Study Center, procedures, measurements and visits, including:
    a. Reside in a proximity to the Study Center that permits prompt appearance at the facility if requested by the Investigator (maximum of 4-hour travel to Study Center), unless neurological examination or admission, if needed, can be arranged promptly at a suitably equipped and staffed alternative facility *and* these arrangements have been discussed and agreed to by the Ionis Medical Monitor
    b. Adequately supportive psychosocial circumstances, in the opinion of the Investigator
    c. Caregiver/trial partner committed to facilitate patient's involvement in the study who is reliable, competent, at least 18 years of age, willing to accompany the participant to select study visits and to be available to the Study Center by phone if needed and who, in the opinion of the Investigator, is and will remain sufficiently knowledgeable of the patient's ongoing condition to respond to Study Center inquiries about the patient, such as providing information related to study outcome measures requiring caregiver input
    d. Adequate visual and auditory acuity for neuropsychological testing
10. Able to read at a level necessary to complete study assessments
11. No evidence or prior diagnosis of general learning disability

Reproductive Status

12. Females must be non-pregnant, non-lactating and either surgically sterile (e.g., bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or post-menopausal (defined as 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the post-menopausal range for the laboratory involved)
13. Males must be surgically sterile, abstinent* or, if engaged in sexual relations with a female of child-bearing potential, must agree to use an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (ISIS 814907 or placebo) or end of the study, whichever is longer

    * Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception.

### *5.1.2 Exclusion Criteria for MAD, Part 1*

Patients meeting any of the following criteria are not eligible for the study:

Target Disease Exceptions

1. First or second degree family member among the investigational or Sponsor staff directly involved in the trial
2. Any contraindication or unwillingness to undergo MRI scanning (e.g., metal implants including MRI incompatible IUDs, claustrophobia, agitation or tremor of a severity that precludes MRI scans)
3. Any contraindication or unwillingness to undergo LP

Medical History and Concurrent Disease

4. Patient receives daily nursing care due to cognitive condition
5. Evidence of clinically relevant neurological disease other than the disease being studied, including
    a. Cerebrovascular disease (history of TIA, stroke, significant vascular disease [large vessel stroke, diffuse white matter hyperintensities {WMHs}, multiple lacunes, bilateral thalamic lesions, and/or > 5 microhemorrhages on brain MRI] or modified 8-item Hachinski Ischemia Scale score ≥ 4)
        i. In addition to microhemorrhages, the degree of WMH severity will be centrally rated on T2 FLAIR and GRE T2 star images using the Age Related White Matter Changes (ARWMC) scale (e.g., WMHs > 5 mm, rated on a 4-point scale ranging from 0 (no lesions) to 3 (diffuse involvement of the entire region), within 5 regions in each hemisphere; a score of 3 in a region constitutes the presence of diffuse WMH)

ii. Multiple lacunes are rated as the presence of at least 2 lacunes in the basal ganglia and at least 2 lacunes in the frontal white matter. To meet the criterion for the presence of bilateral thalamic lesions, at least 1 lesion must to be present in each thalamus

b. Current infectious/metabolic/systemic diseases affecting CNS

c. History of a serious infectious disease affecting the brain in the 5 years prior to Screening

d. History of clinically significant head trauma (i.e., any loss of consciousness for > 5 minutes), including motor vehicle accident and/or concussion in the 3 years prior to Screening

e. MRI scan at Screening shows evidence for a potential alternative etiology for dementia (i.e., non-AD etiology)

f. History of generalized seizures in the 3 years prior to Screening

6. Psychiatric diagnosis/symptoms interfering with assessment of cognition

   a. Attempted suicide, suicidal ideation with a plan that required hospital admission and/or change in level of care within 6 months prior to Screening. For patients with (i) a suicide ideation score ≥ 4 on the Columbia Suicide Severity Rating Scale (C-SSRS) within the last 6 months, or (ii) suicidal behaviors within the last 6 months (as measured by the answer "Yes" on any of the C-SSRS Suicidal Behavior Items, a risk assessment should be done by an appropriately-qualified mental health professional (e.g., a Psychiatrist or licensed Clinical Psychologist) to assess whether it is safe for the patient to participate in the study. Patients deemed by the Investigator to be at significant risk of suicide should be excluded

   b. Major depressive episode within 6 months prior to Screening (with the exception of patients in remission on allowed concomitant antidepressant medication) or at risk for psychosis, confusional state or violent behavior in the opinion of the Investigator

   c. Geriatric Depression Scale Short Form > 6

   d. History of alcohol or drug dependency/abuse within 3 years prior to Screening

7. Clinically significant cardiac conditions including cardiac failure, angina or previous acute coronary syndrome within 6 months of Screening

8. Ongoing or recent (within 12 weeks of Screening) uncontrolled, clinically significant medical condition including:

   a. Hematological, hepatic, diabetes, hypertension, thyroid or endocrine disease, gastrointestinal disease, dialysis, or abnormal renal function

   b. Retinal impairment or disease that would interfere with the ability to comply with study procedures

   c. Peripheral vascular disease that would interfere with the ability to comply with study procedures

d. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C, chronic hepatitis B consistent with CDC interpretation of serology panel or syphilis

9. History of bleeding diathesis or coagulopathy and/or platelet count < LLN at Screening
10. A medical history of brain or spinal abnormalities by MRI/computed tomography (CT) or history that might interfere with the LP process, CSF circulation or safety assessment, including subarachnoid hemorrhage, suggestions of raised intracranial pressure on MRI or ophthalmic examination, spinal stenosis or curvature, spina bifida occulta, Chiari malformation, hydrocephalus, syringomyelia, tethered spinal cord syndrome, frontotemporal brain sagging syndrome and connective tissue disorders such as Ehlers-Danlos syndrome and Marfan syndrome.
11. Any medical condition that increases risk of meningitis unless patient is receiving appropriate prophylactic treatment
12. History of malignancy within 5 years prior to Screening, except for adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, localized prostate carcinoma. Patients with other malignancies that have been treated with potentially curative therapy with no evidence of recurrence for ≥ 5 years post-therapy may also be eligible if approved by the Sponsor Medical Monitor
13. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed 3 days prior to Part 1, Day -1
14. At Screening, have any condition such as medical, psychiatric or neurological other than the tauopathy under study which, in the opinion of the Investigator or Sponsor, would make the patient unsuitable for inclusion, or could interfere with the patient participating in or completing the study

Prohibited and Restricted Medications and Procedures

15. Treatment with another investigational product (drug biological agent or device) within 1 month of Screening, or 5 half-lives of investigational agent, whichever is longer
16. Use of a disallowed CNS-active or antipsychotic medication within 4 weeks or 5 half-lives (whichever is greater) prior to the start of Screening
17. Change in dose regimen of an allowed CNS-active or antipsychotic medication within 4 weeks or 5 half-lives (whichever is greater) prior to the start of Screening
18. Change in dose regimen of a cholinesterase inhibitor or memantine within 8 weeks prior to the start of Screening
19. Change in dose regimen of estrogen replacement therapy within 4 weeks prior to the start of Screening
20. Change in dose regimen of nutraceuticals or supplements within 4 weeks prior to the start of Screening
21. Use of warfarin
22. Use of Neudexta (dextromethorphan and quinidine)

23. Prior treatment with an active immunotherapy agent targeting the CNS
24. Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter
25. Any medical or surgical procedure involving general anesthesia within 12 weeks of Screening or planned during the study
26. Any history of gene therapy or cell transplantation or any experimental brain surgery

Physical and Laboratory Findings

27. Clinically significant laboratory, vital sign or ECG abnormalities at Screening (including HR < 45 bpm, SBP < 90 mmHg and confirmed BP readings > 170/105 mmHg)
28. Any hepatic, glucose, renal, hematology or thyroid laboratory tests above or below the limits of normal that are considered to be clinically significant must be discussed with the Sponsor Medical Monitor
29. Clinically significant B12 or folate deficiencies at Screening or previous deficiencies that have not been corrected for at least 12 weeks prior to Screening

## 5.2 Eligibility for Long-Term Extension, Part 2

### *5.2.1 Inclusion Criteria for LTE, Part 2*

*This section is only applicable to patients from Cohorts A and B, as patients from Cohort C and D will seamlessly transition to Part 2.*

Patients from Cohorts A and B must meet the following inclusion criteria to be eligible:

Target Population

1. Able to read, understand, and provide written informed consent (signed and dated)
2. Able and willing to meet all study requirements in the opinion of the Investigator, including:
    a. Adequately supportive psychosocial circumstances
    b. Caregiver/trial partner committed to facilitate patient's involvement in the study who is reliable, competent, at least 18 years of age, willing to accompany the participant to select study visits, and to be available to the Study Center by phone if needed, and who, in the opinion of the Investigator, is and will remain sufficiently knowledgeable of the patient's ongoing condition to respond to Study Center inquiries about the patient, such as providing information related to study outcome measures requiring caregiver input
    c. Adequate visual and auditory acuity for neuropsychological testing
    d. Able to tolerate blood draws and lumbar punctures
3. Must have completed both the Treatment Evaluation Period and Post-Treatment Period in Part 1

Reproductive Status

4. Females must be non-pregnant, non-lactating and either surgically sterile (e.g. bilateral tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or post-menopausal (defined as 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the post-menopausal range for the laboratory involved)
5. Males must be surgically sterile, abstinent*, or if engaged in sexual relations with a female of child-bearing potential, must agree to use and acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug ISIS 814907 or end of study, whichever is longer.

* Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception.

### *5.2.2 Exclusion Criteria for LTE, Part 2*

*This section is only applicable to patients from Cohorts A and B, as patients from Cohort C and D will seamlessly transition to Part 2*

Prohibited and restricted Medications and Procedures

1. Treatment with another investigational product (drug, biological agent, or device) within 1 month of Registration, or 5 half-lives of investigation agent, whichever is longer
2. Use of a disallowed CNS-active or antipsychotic medication within 4 weeks or 5 half-lives (whichever is greater) prior to Registration
3. Change in dosing regimen of an allowed CNS-active or antipsychotic medication within 4 weeks or 5 half-lives (whichever is greater) prior to Registration
4. Change in dose regimen of a cholinesterase inhibitor or memantine within 8 weeks prior to Registration
5. Change in dose regimen of estrogen replacement therapy within 4 weeks prior to Registration
6. Change in dose regimen of nutraceuticals or supplements within 4 weeks prior to Registration
7. Use of warfarin
8. Use of Neudexta (dextromethorphan and quinidine)
9. Prior treatment with an active immunotherapy agent targeting the CNS
10. Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter
11. Any medical or surgical procedure involving general anesthesia within 12 weeks of Registration or planned during the study
12. Any history of gene therapy or cell transplantation or any experimental brain surgery

Medical History and Concurrent Disease

13. Have any other condition which, in the opinion of the Investigator or Sponsor, would make the patient unsuitable for the inclusion or could interfere with the patient participating in or completing the study

# 6. STUDY PROCEDURES

## 6.1 Study Schedule

All required study procedures are outlined in Appendices A, B, and C. Additional patient visits may be scheduled if required for further evaluation of an abnormal laboratory value or a reported AE.

All reasonable attempts should be made to ensure compliance with the visit schedule and visit windows as outlined in Appendix A. However, in the event that a visit does not occur or is delayed, all subsequent visits should be calculated based on the time elapsed since the first dosing day in each Part of the study rather than from the date of the previous visit. Specifically, while patients are in the MAD, Part 1, of the study, all subsequent visits should be calculated based on the time elapsed since Day 1 in Part 1; once patients have entered the LTE, Part 2, of the study all subsequent visits should be calculated based on the time elapsed since Day 1 in Part 2.

### *6.1.1 Multiple Ascending Dose, Part 1*

#### *6.1.1.1 Screening Period (Week -8 to Week -1)*

Written informed consent for the study will be obtained prior to the performance of any study-related procedures including screening procedures. During the Screening Period, inclusion/exclusion criteria will be evaluated to determine patient eligibility for the study. Abnormal laboratory screening results may be retested for review by the Study Medical Monitor for eligibility purposes. Personal information will also be collected including race, ethnicity, sex, and date of birth as part of the demographic information for all screened patients during the screening period.

#### *6.1.1.2 Treatment Evaluation Period (Week 1 to Week 14)*

Study Drug will be administered four times, with doses separated by 28 days (Section 8.1). In the event of a dosing interval change in Cohort D, Study Drug will be administered 2 times, with doses separated by 84 days.

Treatment Evaluation Period procedures are tabulated in Appendices A and C. Eligible patients will report to the Study Center on Day -1 (the day prior to first Study Drug administration) for assessments. Assessments should be completed at approximately the same time of day from visit to visit. At the completion of assessments on Day -1, patients will be discharged unless the Investigator feels it is in the patient's best interest for him/her to remain in the Study Center overnight. Patients will return to the Study Center on Day 1 to undergo CSF sampling and Study Drug administration via LP, followed by overnight observation in the Study Center, safety assessments on Day 2 and then discharge. On Day 3, the Study Center will conduct a brief visit with the patients by phone to capture any adverse events or changes in concomitant medication usage. On Day 8, the patients will return to the Study Center for additional assessments.

Each subsequent Study Drug administration will be conducted in the same manner, with most pre-dose assessments conducted on the day before Study Drug administration; post-dose, in-clinic observation of at least 6 hours after Study Drug administration (longer or overnight if deemed appropriate by the Investigator); in-clinic assessments on the day after Study Drug administration; telephonic contact with patients 2 days after Study Drug administration and in-clinic or telephonic assessments one week after Study Drug administration as defined in Appendix A.

#### *6.1.1.3 Post-Treatment Period (Week 15 to Week 37) or Early Termination*

After completion of the Treatment Evaluation Period, patients will enter the 23-week Post-Treatment Period. This period consists of 4-5 Study Center visits on Weeks 17, 21, 25, 29 (Cohorts C and D only), and 37, as outlined in the Schedule of Procedures in Appendix A.

Patients in Cohorts A and B will complete all visits up to Day 253 in Part 1 and will enter Part 2 of the study after the FSMG has reviewed the Part 1 Cohort C data during the dose-escalation meeting to Cohort D (2/3 of patients in Cohort C having received all doses of Study Drug in Part 1); therefore there will be a variable gap of time between the end of Part 1 and entry into Part 2 for those patients.

Patients in Cohorts C and D will seamlessly transition from Part 1 into Part 2 after completing all visits up to Day 253 in Part 1. The Part 1 Day 253 visit will correspond to the Part 2 Day -1 visit.

Patients who discontinue Study Drug in the Treatment Evaluation Period of Part 1 should complete any follow-up visits associated with the most recent administration of Study Drug (see Section 8.9) and should be encouraged to complete the Part 1 Post-Treatment Period. Patients who prematurely discontinue the Treatment Evaluation, or the Post-Treatment Periods, in Part 1, and patients whose treatment assignment has been unblinded during Part 1 due to a safety issue, will not be allowed to participate in Part 2.

### *6.1.2 Long-Term Extension, Part 2*

#### *6.1.2.1 Registration Period (Week -3 to Week -1)*

*This section is only applicable to patients from Cohorts A and B, as patients from Cohort C and D will seamlessly transition to Part 2.*

Written informed consent will be obtained from patients in Cohorts A and B returning for LTE, Part 2, of the study prior to the performance of any study-related procedures. During the Registration Visit, inclusion/exclusion criteria will be evaluated to determine patient eligibility for the study. Any changes in medical history, and concomitant medications, that occurred between the end of Part 1 and entry into Part 2 will be recorded.

#### *6.1.2.2 Treatment Evaluation Period (Week 1 to Week 48)*

ISIS 814907 will be administered 5 times during the LTE, with doses given quarterly (84-day interval; Section 8.1).

The Part 2 Treatment Evaluation Period procedures are tabulated in Appendices A and C. Eligible patients will report to the Study Center on Day -1 (the day prior to first administration of ISIS 814907) for assessments. Assessments should be completed at approximately the same time of day from visit to visit. At the completion of assessments on Day -1, patients will be discharged unless the Investigator feels it is in the patient's best interest for him/her to remain in the Study Center overnight. Patients will return to the Study Center on Day 1 to undergo CSF sampling and ISIS 814907 administration via LP, followed by overnight observation in the Study Center, safety assessments on Day 2 and then discharge. On Day 3, the Study Center will conduct a brief visit with the patients by phone to capture any adverse events or changes in concomitant medication usage. On Day 8, the patients will return to the Study Center for additional assessments.

Each subsequent administration of ISIS 814907 will be conducted in the same manner, with most pre-dose assessments conducted on the day before administration of ISIS 814907; post-dose, in-clinic observation of at least 6 hours after administration of ISIS 814907 (longer or overnight if deemed appropriate by the Investigator); in-clinic assessments on the day after administration of ISIS 814907; telephonic contact with patients 2 days after administration of ISIS 814907 and in-clinic or telephonic assessments one week after administration of ISIS 814907 as defined in Appendix A.

#### *6.1.2.3 Post-Treatment Period (Week 49 to Week 64) or Early Termination*

After completion of the Treatment Evaluation Period, patients will enter the 16-week Part 2 Post-Treatment Period. This period consists of 2 Study Center visits on Weeks 60 and 64, as outlined in the Schedule of Procedures in Appendix A.

Patients who terminate early from the Part 2 Treatment Evaluation or Post-Treatment Periods (for reasons other than withdrawal of consent) should be encouraged to submit to additional visit(s) as described in detail in Section 8.9 (also see Appendices A and C and Study Design and Treatment Schema).

### 6.2 Study Assessments

The order of study assessments will be defined in the Study Manual. All efforts should be made to adhere to a consistent order of assessments throughout the study. Rest periods will be scheduled during the testing, and the patient should be permitted additional rest periods as needed to minimize testing fatigue.

#### *6.2.1 International Standard Classification of Education (ISCED)*

The ISCED is used to capture each patient's level of education based on categories ranging from pre-primary education through advanced degree programs.

#### *6.2.2 Columbia Suicide Severity Rating Scale (C-SSRS)*

The C-SSRS is a structured tool to assess suicidal ideation and behavior. Four (4) constructs are measured: severity of ideation, intensity of ideation, behavior and lethality of actual suicide attempts. Binary (yes/no) data are collected for 10 categories, and composite endpoints based on the categories are followed over time to monitor patient safety (Posner et al. 2011). It maps to the Columbia-Classification Algorithm for Suicide Assessment (C-CASA) and meets the criteria

listed in the recent FDA draft guidance for assessment of suicidality in clinical trials (FDA Sep 2010). The C-SSRS will be used to assess eligibility for the study and to monitor the patients throughout the study.

A referral for psychiatric evaluation is required for any increase (even if apparently transient) in the suicidal ideation score from baseline to a level that would have been exclusionary for this study. In any event of suspected active suicidal intent or significant suicidal behavior or clinical finding suggesting that the patient is dangerous to himself/herself, the patient should be referred for immediate psychiatric evaluation.

### *6.2.3 Vital Signs Measurement*

Vital signs are to be measured at visits indicated in Appendix A. Refer to the manufacturer's manual for proper operation, calibration, care and handling of the monitor. Select an appropriately sized BP cuff.

For each vital sign measurement, record the patient's position and the arm used for the measurement.

#### *6.2.3.1 Seated Blood Pressure Measurement*

Situate the patient in a quiet environment with feet flat on the floor, back against the chair and arm resting on a table or other support so that the midpoint of the cuff is at the level of the heart. The patient must rest for at least 10 minutes in the seated position prior to measuring blood pressure (BP).

#### *6.2.3.2 Standing Blood Pressure Measurement for Orthostatic Assessment*

To assess for the presence of orthostatic hypotension, additional BP and pulse rate will be assessed at selected study visits (see Appendix A) or as needed at the discretion of the Investigator. After measurement of seated BP, the patient will change to a standing position. After 2 minutes of standing, BP and pulse rate will be measured three times, with each test separated by at least 1 minute from the prior test. If the diastolic BP readings from the 3 tests are not all within 5 mm Hg, 2 additional standing BP readings must be obtained (total of 5 BP readings), with each test separated by at least 1-minute from the prior test.

### *6.2.4 Electrocardiogram*

A standard 12-lead electrocardiogram (ECG) will be recorded at selected study visits (see Appendix A). Each ECG will be performed in triplicate. A central ECG service will be utilized for reading all ECGs. Refer to the ECG Manual for proper operation, care and handling of the machine.

### *6.2.5 Physical/Neurological Examination*

Neurological examinations include assessment of mental status, level of consciousness, sensory function, motor function, cranial nerve function and reflexes. Neurological examinations will be performed at the times/dates according to the schedule as shown in Appendix A (Schedule of Procedures).

### *6.2.6 Physical Measurements (Height and Weight)*

Height will be measured at Screening in the MAD, Part 1, of the study only. For measurements of body weight, the same weighing scales should be used to weigh a given patient throughout the study. Scales should be calibrated and reliable; scales should be zeroed just prior to each patient's weigh-in session. A patient should void just prior to being weighed. Weight should be recorded before a patient's meal (if applicable) and at approximately the same time of day at each visit. Patients should be minimally clothed (i.e., no shoes or heavy over-garments).

### *6.2.7 Neuroimaging Assessments*

Neuroimaging assessments will be conducted using a 3T MRI scanner or PET scanner.

A 3D T1-weighted structural MR scan will be used to quantitate whole brain, hippocampal, and intraventricular volumes.

MRI safety sequences (T2 FLAIR, GRE T2 star, T2 Fast Spin Echo [FSE]/Turbo Spin Echo [TSE] and DTI) will be performed at Screening and Day 169 in MAD Part 1 and at the Registration Visit (patients who are not seamlessly transitioning to the LTE Part 2 only), Day 252 (or Day 336 if not performed at Day 252) and Day 449 in LTE Part 2, to characterize the patients' pre-treatment and post-treatment state. Safety scans must be reviewed locally by a trained radiologist.

To quantify the CSF volumes of individual patients, an MRI scan of the entire neuroaxis will be obtained at Screening.

Non-ionizing arterial spin labeling (ASL) MRI will be used to quantitate changes in tissue perfusion.

Positron emission tomography (PET) imaging will be used to visualize brain changes; in the MAD, Part 1, of the study PET imaging will only be done in Cohorts C and D, and in LTE, Part 2, of the study PET imaging will be done in all patients. At each PET imaging visit, each patient will undergo PET imaging with only 1 of 2 ligands; either a fluorodeoxyglucose (FDG) tracer will be used to capture the changes of regional metabolism in the brain, or MK6240, a Tau ligand, to capture changes in Tau pathology. For Cohorts C and D, PET imaging will be done 3 times over the course of the study: during the MAD, Part 1 screening window, at the Part 1 Day 169 visit, and at the Part 2 Day 449 visit. For patients from Cohorts A and B returning to participate in Part 2, PET imaging will be at 2 timepoints, during the Part 2 Registration Period and at the Part 2 Day 449 visit. In the event that Tau-PET is either not available at the site or has not yet been approved, then FDG-PET should be performed. As soon as Tau-PET is approved and available at a site, patients should switch to Tau-PET imaging, instead of FDG-PET imaging, for their next scan.

### *6.2.8 Collection of CSF*

Throughout the study, CSF will be collected at Screening, pre-dose on all Study Drug dosing days in Parts 1 and pre-dose on all ISIS 814907 dosing days in Part 2, and during the Post-Treatment Periods of Part 1 and 2 as described in Appendix A. At Screening, 12 mL of CSF fluid will be collected using the provided LP collection kit. This sample will be utilized for screening tests (Aβ42, total tau, and p-tau) and for biomarker testing as outlined in Appendix B.

At CSF collections in subsequent visits, 20 mL of CSF fluid will be collected using the provided LP collection kit to allow for biomarker, safety, and PK testing. Depending on institutional guidelines, local anesthesia may be used for the procedure. Sedation may not be used. Spinal ultrasound may be used for the LP procedure, if deemed necessary, but is not required. Fluoroscopy guidance may be used if attempts at LP without imaging are unsuccessful.

#### *6.2.9 Laboratory Assessments*

Laboratory analyte samples will be collected throughout the study. A list of these analytes is contained in Appendix B.

##### *6.2.9.1 Plasma, Serum and Urinalysis Laboratory Assessments*

Routine chemistry, hematology and urinalysis panels will be conducted as indicated in the Schedule of Assessments (Appendix A). PK analysis of ISIS 814907 in plasma will be conducted using samples collected as described in Appendices A and C. FSH will be measured at Screening in females who are not documented as surgically sterile.

In addition, assessments of exploratory biomarkers will include neurofilament light chain (NfL), tau, interleukin-6 (IL-6), TNFα and 24S-hydroxycholesterol.

A thyroid panel and levels of uric acid, folate, B12, and homocysteine will be measured at the Screening visit only. Other screening tests include hepatitis, HIV and drug/alcohol tests as shown in Appendix B.

Coagulation tests (prothrombin time [PT], INR and activated partial thromboplastin time [aPTT]) and platelets will be analyzed at the central laboratory, as shown in Appendix A. In addition, for each scheduled LP, local laboratory analysis of PT, INR, aPTT, and platelets must be conducted, and results reviewed prior to performing the LP.

- For dosing visits, collection for local labs may occur on the day prior to dosing at the same time that samples are collected for analysis at the central laboratory
- At Screening, analysis of PT, INR, aPTT, and platelets must be conducted, and results reviewed within 2 days prior to the Screening LP
- For other visits requiring LP (Part 1, Days 113, and 141 for Cohorts A and B, and Days 141 and 197 for Cohorts C and D; Part 2, Day 421), collection for local labs may occur on the day of the LP provided results can be obtained and reviewed prior to performing the LP

Extra serum will be stored at -80 °C for follow-up exploration of laboratory findings and/or adverse events as noted in Appendix A.

##### *6.2.9.2 CSF Laboratory Assessments*

CSF will be used for standard laboratory measurement of cells, glucose, protein, albumin and ISIS 814907 concentration analyses. CSF will also be used for determining patient eligibility for the study.

Total tau in CSF is the key exploratory endpoint for the study. Other exploratory CSF biomarkers will be examined. Potential biomarkers include, but are not limited to NfL (a neuronal injury marker); p-tau (a target engagement marker); VILIP1 (a neuronal injury marker); chromogranin B, neurogranin and SNAP25 (synaptic markers); IL-6, TNFα, IL-1β, MCP-1, S100 calcium binding protein B (S100B) and YKL-40 (innate immune activation markers); C3 and FH (complement); apolipoprotein E and clusterin.

Levels of homocysteine, B12, and folate will be measured at the Screening and Part 1, Day 1 visits only.

Extra CSF will be stored for investigation of possible biomarkers of tauopathy, the PD effects of ISIS 814907, or for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, immunogenicity assessments (including assay development and validation purposes), or to assess other actions of ISIS 814907 with CSF constituents.

#### *6.2.9.3 Genetic Testing*

Genetic tests will be conducted as described in the Schedule of Assessments (Appendix A).

All patients will undergo genetic testing for *APP*, *PSEN1*, *PSEN2, H1 MAPT haplotype* and for common SNPs of *APOE, IL1RAP,* and *BCHE*-associated with risk for developing AD. Tests do not need to be repeated if conducted previously and a laboratory report is available for documentation of results.

The apolipoprotein E4 variant (APOE ε4) is the largest known genetic risk factor for late-onset sporadic AD, and research suggests APOE ε4 and the butyrylcholinesterase-K variant (BCHE-K; rs1803274) of the *BCHE* gene interact synergistically to promote AD risk (Lane et al. 2008; Lane and Darreh-Shori 2015; De Beaumont et al. 2016). In a GWAS investigation of the Alzheimer's disease neuroimaging initiative's MCI/mild AD cohort, a mutation in the 5′ untranslated region of the *BCHE* gene (rs509208) was shown to be an independent and substantial contributor to cortical fibrillar Aβ burden in humans (Ramanan et al. 2014). Together, *APOE* and *BCHE* loci explained 15% of the variance in cortical Aβ levels (*APOE* 10.7%, *BCHE* 4.3%).

An association with higher rates of amyloid accumulation independent from *APOE* (apolipoprotein E) ε4 status was identified in *IL1RAP* (interleukin-1 receptor accessory protein; rs12053868-G) (Ramanan et al. 2015). *IL1RAP* rs12053868-G carriers were more likely to progress from MCI to Alzheimer's disease and exhibited greater longitudinal temporal cortex atrophy on MRI (Ramanan et al. 2015). In independent cohorts rs12053868-G was associated with accelerated cognitive decline and lower cortical $^{11}$C-PBR28 PET signal, a marker of microglial activation.

An inversion polymorphism of approximately 900kb on Chromosome 17q21 and including the *MAPT* gene resulted in 2 haplotypes, H1 and H2. SNPs characteristic of the H1 haplotype will be used to identify its presence or absence.

#### *6.2.9.4 Immunogenicity Testing*

Plasma samples for evaluation of the presence of anti-ISIS 814907 antibodies will be collected pre-dose throughout Parts 1 and 2 of the study as listed in the Schedule of Procedures. No assay currently exists for evaluation of these samples for the presence of anti-ISIS 814907 antibodies. Therefore, these samples will be stored for potential future analysis, as appropriate, at a time when a suitable assay becomes available.

### *6.2.10 Cognitive and Neuropsychiatric Tests*

#### *6.2.10.1 Mini-Mental State Examination*

The Mini-Mental State Examination (MMSE) is used to quantify cognitive function and to screen for cognitive loss. It is a severity scale, not a diagnostic scale, and can be confounded by level of education such that dementia may be present and diagnosed despite relatively high MMSE score. The test administrator presents the patient with a series of questions and tests related to orientation, attention, calculation, recall, language and motor skills with a maximum possible score of 30 points. Eligibility for the MAD, Part 1, of the study is contingent on MMSE score (see Section 5.1). When patients from Cohorts A and B are invited back to the LTE, Part 2, of the study, Part 2 eligibility is not contingent on MMSE score.

#### *6.2.10.2 Modified Hachinski Ischemia Scale*

The MHIS is used at Screening to exclude patients with dementia likely due to vascular factors (Hachinski et al. 2012). The Investigator assesses vascular involvement using a 12-point, 8-item scale: abrupt onset, stepwise deterioration, somatic complaints, emotional incontinence, hypertension (past or present), history of stroke, focal neurological symptoms, focal neurological signs. Abrupt onset of dementia, history of strike, focal neurological symptoms and focal neurological signs each contribute 2 points to the scale; the other items each contribute 1 point to the scale. Patients with total scores greater than or equal to 4 are ineligible for the MAD, Part 1, of the study. When patients from Cohorts A and B are invited back to the LTE, Part 2, of the study, eligibility is not contingent on MHIS score.

#### *6.2.10.3 Clinical Dementia Rating (CDR) Scale*

The Clinical Dementia Rating (CDR) is a global scale used at Screening to categorize the severity of Alzheimer's type dementia (Morris 1993; Morris 1997). It utilizes a semi-structured test administrator interview with the patient and the trial partner to obtain the information necessary to rate the patient's cognitive performance in 6 domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Categorical scores for each domain are 0 (none), 0.5 (questionable), 1 (mild), 2 (moderate) and 3 (severe). A summed total score (sum of boxes) is produced, and a global score (using the same 5 grades of dementia) is derived from the category scores according to the practice described by Morris (Morris 1993). To be eligible for the MAD part, Part 1, of the study, patients need to have a CDR of 1, or a CDR of 0.5 with a memory score of 1. For patients from Cohorts A and B who are invited back to the LTE part, Part 2, of the study, eligibility is not contingent on CDR score.

#### *6.2.10.4 Geriatric Depression Scale Short Form (GDS-SF)*

The GDS-SF is a brief questionnaire in which the test administrator asks patients to respond "yes" or "no" to 15 questions related to how they feel on the day of administration (Yesavage et al. 1982; Sheik and Yesavage 1986). It is administered at Screening. For each question, the response suggestive of depression is scored as one point and the response not suggestive of depression is scored as zero points. The GDS-SF may be used with healthy, medically ill and mild to moderately cognitively impaired older adults. It has been extensively used in community, acute and long-term care settings. Patients with GDS-SF scores greater than six are ineligible for the MAD, Part 1, of the study. When patients from Cohorts A and B are invited back to the LTE, Part 2, of the study, eligibility is not contingent on GDS-SF score.

#### *6.2.10.5 Functional Activities Questionnaire (FAQ)*

The FAQ is a widely-used scale to assess activities of daily living in patients with mild AD (Brown et al. 2011; Marshall et al. 2011). It is a brief questionnaire in which the trial partner rates the patient's abilities in ten areas, such as keeping track of current events and preparing a balanced meal, on a scale of 0 (normal) to 3 (dependent). A score of 30 represents maximal dependence, and a score of 0 represents complete independence (Pfeffer et al. 1982).

#### *6.2.10.6 Neuropsychiatric Inventory – Questionnaire (NPI-Q)*

The Neuropsychiatric Inventory (NPI) assesses behavioral disturbances occurring in dementia patients to evaluate a wide range of psychopathology and distinguish among different etiologies of dementia (Cummings 1997). The NPI-Questionnaire (NPI-Q) is a brief questionnaire form of the NPI intended to identify clinically significant neuropsychiatric disturbances and their associated impact on caregivers (Kaufer et al. 2000). It is completed by the test administrator after discussion with the trial partner about the presence/absence in the patient of 12 behaviors (e.g., anxiety, disinhibition, agitation/aggression) and, for each behavior that is present, its severity (scale of 1-3, with 3 being the most severe) and the associated caregiver distress (scale of 0-5, representing no distress through extreme distress).

#### *6.2.10.7 Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)*

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is a neurological assessment designed to identify abnormal cognitive decline in older adults and to differentiate between different dementia etiologies (Randolph et al. 1998). The RBANS has been shown to correlate with functional limitations in dementia populations (Hobson et al. 2010) and to adequately detect cognitive impairment associated with AD (Duff et al. 2008).

The assessment yields 5 index scores, 1 for each of the domains tested: attention, visuospatial/constructional abilities, language, immediate memory and delayed memory. The index scores for the domains can be used to determine a total scale score.

### 6.3 Restriction on the Lifestyle of Patients

#### *6.3.1 Contraception Requirements*

Use of an acceptable contraceptive method is required for male patients and female partners of male patients (if the female partner is of child-bearing potential). An acceptable contraceptive

method must be used from the time of signing ICF until at least 13 weeks after the last dose of Study Drug or end of the study, whichever is longer.

For the purposes of this study, women of childbearing potential are defined as females who have experienced menarche and do not meet 1 of the following conditions:

- Postmenopausal: 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the postmenopausal range
- Post-surgical sterilization: at least 6 weeks after surgical bilateral tubal occlusion, hysterectomy, bilateral salpingectomy or bilateral oophorectomy with or without hysterectomy

For the purposes of the study, acceptable contraception methods are as follows:

- Male vasectomy with negative semen analysis at follow-up
- Female hormonal contraception
- Female intrauterine contraception/device
- Any double-barrier method*, such as:
  - A combination of a male condom with a female diaphragm, sponge or cervical cap**
  - A combination of a female condom with a female diaphragm, sponge or cervical cap**
  - A combination of a male or a female condom together with spermicidal foam/gel/film/cream/suppository

* A female condom and a male condom should not be used together as friction between the products can result in either or both products failing.

** In countries where spermicide is available, it should be used in addition to these methods since it can further reduce the risk of pregnancy.

Male patients with partners who are pregnant must use condoms as contraception to ensure that the fetus is not exposed to the Study Drug.

All male patients must refrain from sperm donation from the time of signing the informed consent form until at least 13 weeks after the last dose of Study Drug (ISIS 814907 or placebo) or end of the study, whichever is longer.

### *6.3.2 Other Requirements*

Patients should be encouraged to maintain consistency throughout the study with respect to smoking, caffeine consumption and alcoholic beverage consumption.

# 7. STUDY DRUG

## 7.1 Study Drug Description

### *7.1.1 Study Drug Description in MAD, Part 1*

[redacted]

### *7.1.2 Study Drug Description in LTE, Part 2*

[redacted]

**Table 1 Study Drug Characteristics**

| | [redacted] | [redacted] | [redacted] |
|---|---|---|---|
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] |

## 7.2 Packaging and Labeling

[redacted]

## 7.3 Study Drug Accountability

[redacted].

# 8. TREATMENT OF PATIENTS

## 8.1 Study Drug Administration

Study Drug (ISIS 814907 or placebo) dosing will occur at the Study Center on Part 1 Days 1, 29, 57, and 85 for the 4-dose regimen, or Days 1 and 85 for the 2-dose regimen; in Part 2, ISIS 814907 dosing will occur on Days 1, 85, 169, 253, and 337. At each of these visits, the patient will undergo an LP procedure for collection of CSF (see Section 6.2.8) followed by a single IT bolus (2 minute) injection of Study Drug (ISIS 814907 or placebo) in Part 1 or ISIS 814907 in Part 2. A small gauge needle will be used, oriented with the opening rostral (toward the patient's head). The target site for needle insertion is the L3/L4 space but may be 1 segment above or 1-2 segments below this level, if needed.

Depending on institutional guidelines, local anesthesia may be used for the LP procedure. Sedation may not be used. Spinal ultrasound may be used for the LP procedure, if deemed necessary, but is not required. Fluoroscopy guidance may be used if attempts at LP without imaging are unsuccessful.

Table 2 outlines the dose equivalent and ISIS 814907 concentration for delivery for both the MAD and LTE parts of the study. See Section 3.1 for a description of adjustments that might be made to doses and the maximum dose that will be tested.

**Table 2 Study Drug Dosing Information**

| Cohort | Volume to Administer | Nominal ISIS 814907 Concentration | ISIS 814907 Per Dose* |
|---|---|---|---|
| **Study Drug Dosing Information for the MAD, Part 1** | | | |
| Cohort A (4-dose regimen) | 20 mL | 0.5 mg/mL | 10 mg or placebo |
| Cohort B (4-dose regimen) | 20 mL | 1.5 mg/mL | 30 mg or placebo |
| Cohort C (4-dose regimen) | 20 mL | 3.0 mg/mL | 60 mg or placebo |
| Cohort D (4-dose regimen) | 20 mL | 4.5 mg/mL | 90 mg or placebo |
| Cohort D (2-dose regimen) | 20 mL | 5.75 mg/mL | 115 mg or placebo |
| **Study Drug Dosing Information for the LTE, Part 2** | | | |
| Cohorts A, B, and C (quarterly dosing) | 20 mL | 3.0 mg/mL | 60 mg |
| Cohort D (quarterly dosing) | 20 mL | 4.5 mg/mL | 90 mg |
| *Or* Cohort D (quarterly dosing) | 20 mL | 5.75 mg/mL | 115 mg |

* The maximum dose level tested in a cohort will not exceed 115 mg

Please refer to the Study Drug Manual provided by the Sponsor or designee for more detailed instructions for Study Drug and ISIS 814907 preparation and administration. These instructions must be followed for each Study Drug and ISIS 814907 administration.

## 8.2 Other Protocol-Required Drugs

There are no other protocol required drugs. Depending on institutional guidelines, local anesthesia may be used for the LP procedure, following institutional procedures. Sedation may not be used.

## 8.3 Other Protocol-Required Treatment Procedures

There are no other protocol-required treatment procedures.

## 8.4 Treatment Precautions

On Study Drug (ISIS 814907 or placebo) administration days in the MAD, Part 1, of the study and ISIS 814907 administration days in the LTE, Part 2, of the study, patients will be discouraged from resting supine after the LP procedure and will be encouraged to mobilize immediately.

Throughout the study, patients will be monitored for post-LP headache and for any signs or symptoms of infection. The Study Manual will provide guidance for site personnel on differentiating between and managing treatment of pressure headaches and encephalitic/meningitic headaches.

Medications and resuscitation equipment for the emergency management of anaphylactic reactions must be close to the location where the injection is being performed.

## 8.5 Safety Monitoring Rules

Please refer to the Guidance to Investigator section of the Investigator Brochure.

## 8.6 Stopping Rules

Please refer to Section 8.8 for patient stopping rules. Also, please refer to Section 3.7 for a description of cohort and study pausing/stopping rules in the event of one or more reports of dose-limiting adverse events. The Investigator should discuss significant concerns relating to individual patients with the Ionis Medical Monitor to ensure that it is appropriate for the patient to continue Study Drug.

## 8.7 Adjustment of Dose and/or Treatment Schedule

For a given patient, no adjustment of dose is permitted except as mandated by the FSMG as described in Section 3.7. In the event of a concurrent illness that would prevent the dosing procedure from being performed safely, an adjustment in the dose schedule may be permitted at the discretion of the Sponsor Medical Monitor.

## 8.8 Discontinuation of Study Drug

### *8.8.1 Discontinuation in the MAD, Part 1*

A patient must permanently discontinue Study Drug (ISIS 814907 or placebo) treatment for any of the following:

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The patient withdraws consent
- The patient experiences an adverse event that necessitates permanent discontinuation of Study Drug
- The patient experiences a DLT as defined in Section 3.8

The reason for discontinuation of Study Drug (ISIS 814907 or placebo) must be recorded in the electronic Case Report Form (eCRF) and source documentation.

Patients who terminate early from the Treatment Evaluation or Post-Treatment Periods in Part 1 (for reasons other than withdrawal of consent) should be encouraged to submit to additional visit(s) as described in detail in Section 8.9 (also see Appendices A and C and Study Design and Treatment Schema). Patients who prematurely discontinue the Treatment Evaluation Period, or the Post-Treatment Period, in Part 1 will not be allowed to participate in Part 2.

### *8.8.2 Discontinuation in the LTE, Part 2*

A patient must permanently discontinue ISIS 814907 treatment for any of the following:

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4
- The patient withdraws consent
- The patient experiences an adverse event that necessitates permanent discontinuation of ISIS 814907
- The patient experiences a DLT as defined in Section 3.8

The reason for discontinuation of ISIS 814907 must be recorded in the electronic Case Report Form (eCRF) and source documentation.

Patients who terminate early from the Treatment Evaluation or Post-Treatment Periods in Part 2 (for reasons other than withdrawal of consent) should be encouraged to submit to additional visit(s) as described in detail in Section 8.9 (also see Appendices A and C and Study Design and Treatment Schema).

## 8.9 Withdrawal of Patients from the Study

Patients must be withdrawn from the study for any of the following:

- Withdrawal of consent

- The patient is unwilling or unable to comply with the protocol

Other reasons for withdrawal of patients from the study might include:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for noncompliance
- Significant protocol deviation
- Administrative decision by the Investigator or Sponsor

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the eCRF.

Any patient who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request.

For patients withdrawn from the study during the Treatment Evaluation Periods in both Parts 1 and 2 for reasons other than withdrawal of consent, every effort should be made to encourage the patient to (a) conduct the full block of visits associated with the last dose of Study Drug that would have been received had the patient not withdrawn (see description of "visit blocks" below), (b) conduct the visit scheduled for 7 days after the last dose received, (c) and proceed to the Week 17 visit in MAD, Part 1, or the Week 60 visit in LTE, Part 2 approximately 4 weeks after last dose and conduct all visits in the Post-Treatment Period (see Appendix A).

> "Visit blocks": Each dose of Study Drug is associated with a series of visits that are timed to assess acute safety and tolerability of ISIS 814907. In the MAD, Part 1, of the study there are 4 "visit blocks" under the 4-dose regimen: Days -1, 1, 2, and 3; Days 28, 29, 30, and 31; Days 56, 57, 58, and 59; and Days 84, 85, 86, and 87; and there are 2 "visit blocks" under the 2-dose regimen: Days -1, 1, 2, and 3; and Days 84, 85, 86, and 87. In the LTE, Part 2, of the study, there are 5 "visit blocks": Days -1, 1, 2 and 3; Days 84, 85, 86, and 87; Days 168, 169, 170, and 171; Days 252, 253, 254, and 255; and Days 336, 337, 338, and 339.

For patients who terminate early from the Treatment Evaluation Period in Part 1 for reasons other than withdrawal of consent and are not willing to participate in the Post-Treatment Period, every effort should be made to (a) conduct the full block of visits associated with the last dose received (see description of "visit blocks" above), (b) conduct the visit scheduled for 7 days after the last dose received and (c) conduct the Week 37 visit as an Early Termination Visit. Patients who prematurely discontinue the Treatment Evaluation Period, or the Post-Treatment Period, in Part 1 will not be allowed to participate in Part 2.

For patients withdrawn from the study during the Treatment Evaluation Period in Part 2 for reasons other than withdrawal of consent, every effort should be made to encourage the patient to (a) conduct the full block of visits associated with the last dose of ISIS 814907 that would have been received had the patient not withdrawn (see description of "visit blocks" above), (b) conduct the visit scheduled for 7 days after the last dose received, and (c) proceed to the

Week 60 visit approximately 4 weeks after last dose and conduct the next visit in the Post-Treatment Period at Week 64 (see Appendix A).

## 8.10 Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's eCRF. Adverse events related to administration of these therapies or procedures must also be documented on the appropriate eCRF.

### *8.10.1 Concomitant Therapy*

A concomitant therapy is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications and vitamin supplements) administered between date of first dose of study medication and End-of-Study visit.

Patients should consult with the Site Investigator or qualified designee prior to initiating any new medication, including non-prescription compounds or any other non-drug therapy.

**Allowed Concomitant Therapy**

Throughout the study, Site Investigators or designated licensed physicians involved in the study may prescribe concomitant medications or treatments deemed necessary for adverse events or to provide adequate supportive care.

In addition, the following therapies are permitted:

- CNS-active medications lacking significant anticholinergic side effects are allowed if at a stable dose regimen for more than 4 weeks or 5 half-lives (whichever is greater) prior to Screening in Part 1 or Registration in Part 2 (applicable for Cohorts A and B patients only) and the dose regimen is not anticipated to change during the study
- Antipsychotics prescribed for sleep (not psychosis or agitation) are allowed if at a low dose, at a stable dose regimen for more than 4 weeks or 5 half-lives (whichever is greater) prior to Screening in Part 1 or Registration in Part 2 (applicable for Cohorts A and B patients only) and the dose regimen is not anticipated to change during the study
- Cholinesterase inhibitors and memantine are allowed if at a stable dose regimen for more than 8 weeks prior to Screening in Part 1 or Registration in Part 2 (applicable for Cohorts A and B patients only) and the dose regimen is not anticipated to change during the study
- Estrogen replacement therapy is allowed if at a stable dose regimen for more than 4 weeks prior to Screening in Part 1 or Registration in Part 2 (applicable for Cohorts A and B patients only) and the dose regimen is not anticipated to change during the study
- Nutraceuticals and supplements (e.g., fish oil, vitamins, coenzyme Q10, curcumin, creatine) are allowed if at a stable dose regimen for more than 4 weeks prior to Screening in Part 1 or Registration in Part 2 (applicable for Cohorts A and B patients only) and the dose regimen is not anticipated to change during the study
- Aspirin at doses ≤ 325 mg/day is allowed

- Antiplatelet $P2Y_{12}$ inhibitors including clopidogrel, prasugrel, or ticagrelor are allowed. Temporarily withholding antiplatelet therapy before LP should be considered according to local guidelines and investigator clinical judgement on a case by case basis.
- Dual anti-platelet therapy with aspirin and a $P2Y_{12}$ inhibitors is allowed, but aspirin or the $P2Y_{12}$ inhibitor should be temporarily withheld for 7 days before LP according to local guidelines and investigator clinical judgement on a case by case basis
- Direct oral anti-coagulants including apixaban, betrixaban, dabigatran, edoxaban and rivaroxaban are allowed but must be temporarily withheld before LP according to local guidelines and investigator clinical judgement on a case by case basis
- Contraceptive agents are allowed, as described in Section 6.3.1

Depending on institutional guidelines, local anesthesia may be used for the LP procedure. Sedation may not be used.

**Disallowed Concomitant Therapy**

Study patients are prohibited from receiving other experimental agents during the study. This includes marketed agents at experimental doses that are being tested for the treatment of AD. The following agents are specifically prohibited:

- CNS-active medications are not allowed unless non-anticholinergic, at a stable dose regimen for more than 4 weeks or 5 half-lives (whichever is greater) prior to Screening in Part 1 or Registration in Part 2 (applicable for Cohorts A and B patients only) and with a dose regimen that is not anticipated to change during the study
- Antipsychotics are not allowed unless low dose prescribed for sleep (not psychosis or agitation), at a stable dose regimen for more than 4 weeks or 5 half-lives (whichever is greater) prior to Screening in Part 1 or Registration in Part 2 (applicable for Cohorts A and B patients only) and the dose regimen is not anticipated to change during the study
- Cholinesterase inhibitors and memantine are not allowed unless at a stable dose regimen for more than 8 weeks prior to Screening in Part 1 or Registration in Part 2 (applicable for Cohorts A and B patients only) and the dose regimen is not anticipated to change during the study
- Estrogen replacement therapy is not allowed unless at a stable dose regimen for more than 4 weeks prior to Screening in Part 1 or Registration in Part 2 (applicable for Cohorts A and B patients only) and the dose regimen is not anticipated to change during the study
- Nutraceuticals or supplements (e.g., fish oil, vitamins, coenzyme Q10, curcumin, creatine) are not allowed unless at a stable dose regimen for more than 4 weeks prior to Screening in Part 1 or Registration in Part 2 (applicable for Cohorts A and B patients only) and the dose regimen is not anticipated to change during the study
- Warfarin is not allowed
- Active immunotherapy agents targeting the CNS
- Neudexta is not allowed (dextromethorphan and quinidine)

- Sedation is not allowed for any procedures in the study
- Anti-anxiety medication prescribed for imaging-related anxiety is generally not allowed; in cases where an otherwise eligible subject may require minimal sedation for the MRI or PET imaging, a discussion with the Medical Monitor should occur to determine if the use of anti-anxiety medication can be approved

### *8.10.2 Concomitant Procedures*

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between the date of first dose of Study Drug (ISIS 814907 or placebo) and the End-of-Study visit.

For patients in Cohorts A and B, a concomitant procedure could be performed in the MAD, Part 1, of the study between the date of the first dose of Study Drug (ISIS 814907 or placebo) and the Part 1 End-of-Study visit, or in the LTE, Part 2, of the study between the date of first dose of ISIS 814907 and the Part 2 End-of-Study visit. For patients in Cohorts C and D, who will seamlessly transition into Part 2, a concomitant procedure could be performed between the date of the first dose of Study Drug (ISIS 814907 or placebo) in Part 1, and the Part 2 End-of-Study visit.

## 8.11 Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded in the CRF by Study Center staff.

# 9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

## 9.1 Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor or designee in accordance with the SOP for ICSR management throughout the conduct of the clinical trial.

## 9.2 Regulatory Requirements

The Sponsor or designee is responsible for regulatory submissions and reporting to the Investigators of SAEs including suspected unexpected serious adverse reactions (SUSARs) per the International Conference on Harmonization (ICH) guidelines E2A and ICH E6. Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any SAE according to applicable regulations. The FSMG will be notified of any SAE as specified in the FSMG charter.

The Sponsor or designee will evaluate the available information and decide if there is a reasonable possibility that the Study Drug (ISIS 814907 or placebo) caused the SAE and, therefore, meets the definition of a SUSAR.

## 9.3 Definitions

### *9.3.1 Adverse Event*

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

### *9.3.2 Adverse Reaction and Suspected Adverse Reaction*

An adverse reaction is any AE caused by the Study Drug.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

### *9.3.3 Serious Adverse Event (SAE)*

A serious adverse event is any adverse event that in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event

  An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization

  Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

## 9.4 Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the Study (i.e., before informed consent) should be recorded as Medical History and not recorded as

AEs unless the pre-existing condition worsened. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible. For patients from Cohorts A and B who will be invited back for the LTE, Part 2, of the study, there will be a variable gap of time that has elapsed between the end of Part 1 and the beginning of Part 2. The Study Manual will provide specific information on how to record AEs or concomitant medications that may have been started or ended during this gap of time, in order to ascertain proper monitoring of patients.

### *9.4.1 Serious Adverse Events*

In the interest of patient safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to Study Drug) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the informed consent form and stop at the end of the patient's follow-up period. For patients in Cohort A and B, the collection of SAEs in the MAD, Part 1, of the study will begin once the informed consent in Part 1 is signed and will stop at the Part 1 Day 253 visit; and in the LTE, Part 2, of the study, collection of SAEs will begin once the informed consent in Part 2 is signed and will stop at the Part 2 Day 449 visit. For patients in Cohorts C and D, who will seamlessly transition into Part 2, collection of SAEs will begin once the informed consent in Part 1 is signed and will stop at the Part 2 Day 449 visit. When the Investigator is reporting by telephone, it is important to speak to someone in person vs. leaving a message. An Initial Serious Adverse Event Form should be completed, and a copy should be faxed to the Sponsor or designee. The fax number for reporting SAEs can be found in the Study Reference Manual.

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the patient's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree the patient's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

### *9.4.2 Non-Serious Adverse Events*

The recording of non-serious AEs will begin after the patient signs the informed consent form and will stop at the end of the patient's follow-up period. For patients in Cohorts A and B, the recording of non-serious AEs in the MAD, Part 1, of the study will begin once the informed consent in Part 1 is signed and will stop at the Part 1 Day 253 visit; and in the LTE, Part 2, of the study, the recording of non-serious AEs will begin once the informed consent in Part 2 is signed and will stop at the Part 2 Day 449 visit. For patients in Cohorts C and D, who will seamlessly transition into Part 2, the recording of non-serious AEs will begin once the informed consent in Part 1 is signed and will stop at Part 2 Day 449 visit. The Investigator will monitor each patient closely and record all observed or volunteered AEs on the Adverse Event Case Report Form.

### *9.4.3 Evaluation of Adverse Events (Serious and Non-Serious)*

The Investigator's opinion of the following should be documented on the Adverse Event Case Report Form:

#### *9.4.3.1 Relationship to the Study Drug*

The event's relationship to the Study Drug (ISIS 814907 or placebo) in the MAD, Part 1 of study, or ISIS 814907 in the LTE, Part 2, of the study is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of Study Drug, e.g., confirmation by positive re-challenge test
- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and Study Drug (ISIS 814907 or placebo) administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to Study Drug (ISIS 814907 or placebo) administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and Study Drug

#### *9.4.3.2 Severity*

The severity of AEs and SAEs will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010 (refer to Appendix D). Any AE not listed in Appendix D will be graded as shown below. For events that are difficult to categorize, the full CTCAE may be utilized to facilitate categorization.

- **Mild:** The event is easily tolerated by the subject and does not affect the subject's usual daily activities
- **Moderate:** The event causes the subject more discomfort and interrupts the subject's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the subject's usual daily activities

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

#### *9.4.3.3 Action Taken with Study Drug*

Action taken with Study Drug (ISIS 814907 or placebo) in the MAD, Part 1 of study, or ISIS 814907 in the LTE, Part 2, of the study due to the event is characterized by 1 of the following.

- **None:** No changes were made to Study Drug (ISIS 814907 or placebo) administration and dose
- **Permanently Discontinued:** Study Drug was discontinued and not restarted

- **Temporarily Interrupted, Restarted – Same Dose:** Dosing was temporarily interrupted or delayed due to the AE and restarted at the same dose

#### *9.4.3.4 Treatment Given for Adverse Event*

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the Adverse Event Case Report Form. Treatment should also be recorded on the concomitant treatment or ancillary procedures eCRF, as appropriate.

#### *9.4.3.5 Outcome of the Adverse Event*

If the event is a non-serious AE, then the event's outcome is characterized by 1 of the following:

- **AE Persists:** Patient terminates from the trial and the AE continues
- **Recovered:** Patient recovered completely from the AE
- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity (if applicable):** AE severity changed

If the event is an SAE, then the event's outcome is characterized by 1 of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)

### 9.5 Procedures for Handling Special Situations

#### *9.5.1 Abnormalities of Laboratory Tests*

Clinically significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically significant abnormalities will be monitored by the Investigator until the parameter returns to its pre-dose value or until agreement is reached between the Investigator and Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory source document.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents.

### *9.5.2 Prescheduled or Elective Procedures or Routinely Scheduled Treatments*

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the patient's consent to participate in the study and the timing of the procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

### *9.5.3 Dosing Errors*

Study Drug (ISIS 814907 or placebo) errors should be documented as Protocol Deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing Case Report Form. If the patient takes a dose of Study Drug (ISIS 814907 or placebo) that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

**Should an overdose occur**, the Investigator or designee should refer to the Guidance to Investigator's section of the Investigator's Brochure and contact the Sponsor or designee within 24 hours.

### *9.5.4 Contraception and Pregnancy*

Patients must continue to use appropriate contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a male patient makes or believes that he has made someone pregnant during the study, then the Study Center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24 hours** of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported on Follow-up Pregnancy Forms and reported within 24 hours.

Payment for all aspects of obstetrical care, child or related care will be the patient's responsibility.

The progress of the pregnancy of a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, additional follow-up information may be requested for the mother and infant. Follow-up will be performed to the extent permitted by the applicable regulations and privacy considerations.

# 10. STATISTICAL CONSIDERATIONS

## 10.1 Study Endpoints, Subsets, and Covariates

There is no single primary endpoint for assessment of safety and tolerability, the primary objective of this study. This and other important endpoints that will be evaluated are identified in the following sections.

### *10.1.1 Safety and Tolerability Endpoints*

- Physical examination and standard neurological assessment (including fundi)
- Vital signs (HR, BP, orthostatic changes, weight)
- ECG
- AEs and concomitant medications
- Columbia Suicide Severity Rating Scale (C-SSRS)
- CSF safety labs (cell counts, protein, glucose)
- Plasma laboratory tests (clinical chemistry, hematology)
- Urinalysis
- Safety MRI sequences (GRE T2 star, T2 FLAIR, T2 FSE/TSE, DTI)

Clinical assessments and volumetric neuroimaging measures will be used to monitor for unexpected deterioration.

### *10.1.2 Pharmacokinetic Endpoints*

CSF samples will be collected pre-dose on each injection day (Part 1: Days 1, 29, 57, and 85 for the 4-dose regimen, or Days 1 and 85 for the 2-dose regimen; Part 2: Days 1, 85, 169, 253, and 337) and during the Post-Treatment Period (Part 1: Days 113 and 141 for patients in Cohorts A and B, and Days 141 and 197 for patients in Cohorts C and D; Part 2: Day 421) for PK analyses.

Plasma samples will be collected for PK analyses on the following days:

> **Part 1**: Days 1, 2, 29, 57, 85, and 86, during the Treatment Evaluation Period and on Days 113, 141, 169, 197 (patients in Cohorts C and D only) and 253 during the Post-Treatment Period
>
> **Part 2**: Days 1, 2, 85, 169, 253, 337, and 338 during the Treatment Evaluation Period and on Days 421 and 449 during the Post-Treatment Period

Plasma post-distribution drug levels will be measured. $C_{max}$ and area under the curve (AUC) will be determined, and elimination half-life will be assessed where appropriate.

### *10.1.3 Exploratory Endpoints*

All endpoints in the study, including the exploratory endpoints serve as safety measures. While the below endpoints will be monitored for evidence of target engagement or PD effect, they will

also be monitored to ensure the patient does not experience unexpected worsening during the study.

- Biochemical
  - CSF total tau (key exploratory endpoint)
  - Other potential CSF biomarkers include, but are not limited to, target engagement (p-tau), neuronal injury markers (neurofilament light chain [NfL], phospho neurofilament heavy [pNfH], visinin-like protein 1 [VILIP1]), synaptic markers (neurogranin [Ng], chromogranin B, synaptosomal-associated protein 25 [SNAP25]), innate immune activation markers (interleukin-6 [IL-6], tumor necrosis factor alpha [TNFα], interleukin-1 beta [IL-1β], monocyte chemoattractant protein-1 [MCP-1], S100B), chitinase-3-like protein 1 [YKL-40]), complement (C3, factor H [FH]), apolipoprotein E, clusterin and butyrylcholinesterase [BCHE]
  - Potential blood/plasma biomarkers include, but are not limited to NfL, tau, IL-6, TNFα, 24S-hydroxycholesterol and uric acid
- Neuroimaging
  - Structural MRI
    - Hippocampal, whole brain and ventricular volumes
  - Arterial spin labelling (ASL)
  - PET (Cohorts C and D only in Part 1, and all patients in Part 2)
- Clinical
  - Functioning/ability to perform activities of daily living
    - Functional Activities Questionnaire (FAQ)
  - Cognitive
    - Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
    - Mini-mental state examination (MMSE)
  - Neuropsychiatric
    - Neuropsychiatric Inventory - Questionnaire (NPI-Q)

Analyses may explore relationship between parameters and genetic causes of AD (*APP, PSEN1, PSEN2*) or potential genetic modifiers of disease phenotype (commonly occurring risk-associated SNPs of *APOE*, *BCHE*, *IL1RAP* and *MAPT H1* haplotype).

### 10.2 Sample Size Considerations

While there is no statistical rationale for the sample size, it has been selected based on prior experience with generation 2.0 ASOs given by IT bolus injection to ensure that the safety, tolerability, PK, and exploratory PD will be adequately assessed while minimizing unnecessary patient exposure.

## 10.3 Populations

Safety Population: All patients who are randomized and receive at least 1 dose of Study Drug.

Per Protocol Population: All patients who are randomized and receive all doses of the protocol-specified Study Drug (ISIS 814907 or placebo) and who have no significant protocol deviations.

PK Population: All patients who are randomized to ISIS 814907 and receive at least 1 dose of ISIS 814907 and have sufficient sampling to permit PK evaluation.

## 10.4 Definition of Baseline

For vital signs (BP, heart rate (HR), respiration rate, and temperature), baseline will be defined as the average of the values collected prior to first dose. For ECG, baseline will be defined as the average of the triplicate values collected on Part 1, Day -1. For PD biomarker analysis, baseline will be defined as the average of the Screening and Day1 pre-dose values in Part 1. For all other measures and parameters, baseline will be defined as the last non-missing measure prior to the first dose.

For patients participating in the LTE, Part 2 of the study, post-hoc analyses will also be completed where an alternate baseline will be defined as the average of the values collected immediately prior to first dose in LTE, Part 2 for vital signs; as the average of the triplicate values collected immediately prior to first dose in Part 2 for ECG parameters, and as the last non-missing measure collected immediately prior to the first dose in Part 2, for all other measures and parameters to explore safety and PD effect in the LTE.

## 10.5 Interim Analysis

Unblinded interim analyses may be performed and the results summarized by treatment group. Analyses for early cohorts may be utilized to determine the appropriate dose for later cohorts. The results of an analysis of this type will not be shared with patients or Investigators. Details on controlled access to unblinded data will be outlined in the statistical analysis plan (SAP).

An FSMG will be assembled to review safety, tolerability, PK, and target engagement/PD (as needed) data collected during this study. Unblinded statisticians or designees who will not be involved in the study conduct will generate and distribute the data to the FSMG prior to each FSMG meeting. Based on its ongoing assessment of the study data, the FSMG will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the assessments, frequency of review, meeting schedules and controlled access to unblinded data will be outlined in the FSMG charter.

## 10.6 Planned Methods of Analysis

All CRF data, lab data transfers, and any outcomes derived from the data will be provided in the patient data listings. Patient data listings will be presented for all patients enrolled into the study. Descriptive summary statistics including n, mean, median, standard deviation, standard error, interquartile range ($25^{th}$ percentile, $75^{th}$ percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data. Where appropriate, p-values will be reported. All statistical tests will be conducted using 2-sided tests with 5% Type I error rate unless otherwise stated.

Since there are limited placebo-treated patients within each cohort, the placebo-treated patients will be pooled for analysis according to the SAP.

### *10.6.1 Demographic and Baseline Characteristics*

Demographic and baseline characteristics, including individual patient CSF volume, genetic profile, and results of screening laboratory and clinical testing will be summarized using descriptive statistics by treatment group. Patient disposition will be summarized by treatment group. All patients enrolled will be included in a summary of patient disposition.

### *10.6.2 Safety Analysis*

The safety analysis will be conducted on the Safety Population.

Treatment duration and amount of Study Drug received will be summarized by treatment group.

All treatment-emergent adverse events (TEAEs) and SAEs will be summarized for each treatment group using the Medical Dictionary for Regulatory Activities (MedDRA) coding system by system organ class, preferred term, relationship to Study Drug, and severity.

Narratives of "on-study" deaths, serious and significant AEs, including early withdrawals due to AEs, will be provided.

Laboratory tests to ensure patient safety including chemistry panel, hematology panel, CSF safety labs (cell counts, protein, glucose) and urinalysis, etc., will be summarized by study visit for each treatment group. These safety variables will also be presented as change and percent change from baseline over time after Study Drug administration, as appropriate.

Vital sign and ECG measures will be tabulated by treatment group.

Columbia – Suicide Severity Rating Scale will be summarized for each treatment group. Physical examination, standard neurological assessment (including fundi), and clinical and neuroimaging results will be summarized, if appropriate, and listed.

### *10.6.3 Pharmacokinetic Analysis*

The PK analysis will be conducted on the PK Population.

CSF samples will be collected pre-dose on each injection day (Part 1: Days 1, 29, 57, and 85 for the 4-dose regimen, or Days 1 and 85 for the 2-dose regimen; Part 2: Days 1, 85, 169, 253, and 337) and during the Post-Treatment Period visits (Part 1: Days 113 and 141 for patients in Cohorts A and B, and Days 141 and 197 for patients in Cohorts C and D; Part 2 on Day 421) for PK analyses. The CSF concentrations will be summarized using descriptive statistics and the ISIS 814907 half-life in CSF will be calculated, if possible.

Plasma samples will be collected during the Treatment Evaluation Period (Part 1: Days 1, 2, 29, 57, 85, and 86; Part 2: Days 1, 2, 85, 169, 253, 337, and 338), and at each Post-Treatment Period visit (Part 1: Days 113, 141, 169, 197 (for patients in Cohorts C and D only), and 253; Part 2: Days 421 and 449) for PK analyses. Plasma PK parameters will be summarized using descriptive statistics.

Non-compartmental PK analysis of ISIS 814907 in plasma will be carried out on each individual patient data set. $C_{max}$ and the time taken to reach $C_{max}$ ($T_{max}$) will be obtained directly from the concentration-time data. The plasma half-life ($t_{1/2\lambda z}$) associated with the apparent terminal elimination phase will be calculated, if appropriate using available data, from the equation, $t_{1/2\lambda z} = 0.693/\lambda_z$, where $\lambda_z$ is the rate constant associated with the apparent terminal elimination phase. Partial areas under the plasma concentration-time curve from zero time (pre-dose) to selected times (t) after the administration ($AUC_t$) will be calculated using the linear trapezoidal rule.

Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist. Additional details regarding the PK analysis will be described in the SAP.

### *10.6.4 Pharmacodynamic and Exploratory Analysis*

The PD and exploratory analyses, including evaluation of target engagement, will be conducted on the Per-Protocol and Safety Populations.

The key analysis in the MAD, Part 1, of the study is the correlation of CSF trough concentration of ISIS 814907 on Day 85 with change in CSF tau concentration from baseline to final CSF collection. ISIS 814907 dose and PK (CSF trough concentration of ISIS 814907 on Day 85) will be related to target engagement using the change in CSF total tau level from baseline to Day 85 and to each CSF collection in the Post-Treatment Period. In the LTE, Part 2, of the study a key analysis will be the correlation of CSF trough concentrations of ISIS 814907 on Day 337 with change in CSF tau concentration from baseline to final CSF collection. Additional correlations between ISIS 814907 dose or PK (CSF trough concentration of ISIS 814907 on Day 85) and changes in PD endpoints may be produced.

Exploratory evaluations (Section 10.1.3) will be summarized using descriptive statistics by study visit and treatment group. Change and percent change from baseline over time will be summarized as appropriate. Placebo-treated patients will be pooled for analysis. Evaluations of biomarker and clinical evaluations may include dose- and PK-dependent effects and comparisons between patients receiving ISIS 814907 and those receiving placebo. Comparison between ISIS 814907 group and the pooled placebo may be performed in an exploratory manner. In addition, comparison between patients treated with ISIS 814907 from the start of Part 1 vs. placebo patients who only started ISIS 814907 in Part 2 of the study will be investigated to better understand the impact of delayed treatment. The impact of reported genetic modifiers of disease phenotype on study endpoints may be investigated.

Details will be described in the SAP.

## 11. INVESTIGATOR'S REGULATORY OBLIGATIONS

### 11.1 Informed Consent

Alzheimer's disease can cause behavioral changes, and patients who wish to participate in this study may have disturbances in judgment and decision-making that might compromise their capacity to provide informed consent. Evaluating patients' capacity and obtaining informed consent should be performed in a manner/procedure consistent with the institution's policy. To facilitate evaluation of capacity, the Evaluation to Sign Consent questionnaire or similar

technique may be useful (DeRenzo et al. 1998). In cases where the Investigator is uncertain as to whether the patient possesses capacity to consent and further consideration is warranted, the patient may be referred to an independent expert for further assessment of capacity. A prospective patient's consent will be sought only if he or she demonstrates during the consent process an adequate level of understanding of the study, its requirements and its risks.

The written informed consent document should be prepared in the language(s) of the potential patient population based on an English version provided by the Sponsor or designee.

Before a patient's participation in the trial, the Investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study and before any protocol-specific screening procedures or any Study Drug (ISIS 814907 or placebo) are administered. The patient must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records, and the informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed informed consent form should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the patient.

In cases where the Investigator is uncertain as to whether the patient has maintained the capacity to understand their participation in the study, the patient may be referred to an independent expert for further assessment of capacity. The Investigator can discuss the independent assessment with the Study Medical Monitor and determine whether the patient can remain in the study.

### 11.2 Ethical Conduct of the Study

All applicable regulations and guidelines of current Good Clinical Practice (GCP) as well as the demands of national drug and data protection laws and other applicable regulatory requirements must be followed.

### 11.3 Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed informed consent forms, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by the Sponsor or designee before recruitment of patient into the study and shipment of Study Drug. A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor or designee before recruitment of patients into the study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH

GCP Section 4.5.2. The Investigator should also notify the IEC/IRB of SAEs occurring at the Study Center and other AE reports received from the Sponsor or designee, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor or designee.

### 11.4 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. On the case report forms (CRFs) or other documents submitted to the Sponsor or designee, patients should be identified by initials (if permitted by local law) and a patient identification number only. Documents that are not for submission to the Sponsor or designee (e.g., signed informed consent forms) should be kept in strict confidence by the Investigator.

In compliance with Federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

## 12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

### 12.1 Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor or designee. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or the conduct of the trial. The Investigator **must** send a copy of the approval letter from the IEC/IRB to the Sponsor or designee.

### 12.2 Study Termination

The Sponsor or designee reserves the right to terminate the study. The Investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The Investigator/Sponsor or designee should notify the IEC/IRB in writing of the trial's completion or early termination and send a copy of the notification to the Sponsor or designee.

### 12.3 Study Documentation and Storage

An electronic case report form (eCRF) utilizing an Electronic Data Capture application will be used for this study.

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the patient's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence. In this study, eCRFs may not be used as source documents.

The Investigator and Study Center staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with Section 8 of the ICH Guidelines (E6), suitable for inspection at any time by representatives from the Sponsor or designee and/or applicable regulatory authorities. Elements should include:

- Patient files containing completed CRFs, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor or designee
- If drug supplies are maintained at the Study Center, proof of receipt, Study Drug Product Accountability Record, Return of Study Drug Product for Destruction, final Study Drug product reconciliation, and all drug-related correspondence

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor or designee and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor or designee.

### 12.4 Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor or designee is responsible for inspecting the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the CRFs.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this Study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department (or designees). Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor or designee. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor or designee.

The Principal Investigator will sign and date the indicated places on the CRF. These signatures will indicate that the Principal Investigator inspected or reviewed the data on the CRF, the data queries, and the Study Center notifications, and agrees with the content.

### 12.5 Language

Case report forms must be completed in English. Generic names for concomitant medications should be recorded in English if possible, unless it is a combination drug, then record the trade name in English.

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

### 12.6 Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the Informed Consent document.

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# 14. APPENDICES

# Appendix A Schedule of Procedures

## Appendix A A.1. Schedule of Procedures – MAD Part 1, 4-Dose Regimen, Cohorts A and B

| Study Period | Screen | Treatment Evaluation Period (13 Weeks) | | | | | | | | | | | | | | | | | | | | Post-Treatment Period (23 Weeks) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | -8 to -1 | 1 | | | | 2 | 5 | | | | 6 | 9 | | | | 10 | 13 | | | | 14 | 17[1] | 21 | 25 | 37 or ET[1] |
| Day | -57 to -2 | -1 | 1 | 2 | 3 | 8 | 28 | 29 | 30 | 31 | 36 | 56 | 57 | 58 | 59 | 64 | 84 | 85 | 86 | 87 | 92 | 113 | 141 | 169 | 253 |
| Visit Window (days)* | - | 0 | | | | ± 3 | ± 3 | | | | ± 3 | ± 3 | | | | ± 3 | ± 3 | | | | ± 3 | ± 3 | ± 7 | ± 7 | ± 7 |
| Visit Type[2] | cl | cl | cl | cl | ph | cl | cl | cl | cl | ph | cl | cl | cl | cl | ph | ph | cl | cl | cl | ph | ph | cl | cl | cl | cl |
| Study Drug Administration | | | X | | | | | X | | | | | X | | | | | X | | | | | | | |
| Overnight Stay[3] | | | X→ | | | | | X→ | | | | | X→ | | | | | X→ | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Genetic Testing[4] | | X | | | | | | | | | | | | | | | | | | | | | | | |
| International Standard Classification of Education | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Body Weight and Height[5] | X | X | | | | | X | | | | | X | | | | | X | | | | | X | X | X | X |
| Physical & Neurological Exam[6] | X | | X[a] | X[b] | | X | | X[a] | X[b] | | X | | X[a] | X[b] | | | | X[a] | X[b] | | | X | X | X | X |
| Vital Signs (BP, HR)[7], (RR, T) | X | X | X[c] | | | | X | X[c] | | | | X | X[c] | | | | X | X[c] | | | | X | X | X | X |
| Orthostasis Assessment | X | | | | | | | | | | | | | | | | | | | | | | | | X |
| HIV; Hepatitis B & C; serum folate, B12, homocysteine and uric acid, treponema | X | | | | | | | | | | | | | | | | | | | | | | | | |
| FSH[8] | X | | | | | | | | | | | | | | | | | | | | | | | | |
| Chemistry Panel | X | X | | | | | X | | | | | X | | | | | X | | | | | X | X | X | X |
| Hematology | X | X | | | | | X | | | | | X | | | | | X | | | | | X | X | X | X |
| Urinalysis | X | X | | | | | X | | | | | X | | | | | X | | | | | X | X | X | X |

## Appendix A A.1. Schedule of Procedures – MAD Part 1, 4-Dose Regimen, Cohorts A and B *Continued*

| Study Period | Screen | Treatment Evaluation Period (13 Weeks) | | | | | | | | | | | | | | | | | | | | Post-Treatment Period (23 Weeks) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | -8 to -1 | 1 | | | | 2 | 5 | | | | 6 | 9 | | | | 10 | 13 | | | | 14 | 17[1] | 21 | 25 | 37 or ET[1] |
| Day | -57 to -2 | -1 | 1 | 2 | 3 | 8 | 28 | 29 | 30 | 31 | 36 | 56 | 57 | 58 | 59 | 64 | 84 | 85 | 86 | 87 | 92 | 113 | 141 | 169 | 253 |
| Visit Window (days)* | - | 0 | | | | ± 3 | ± 3 | | | | ± 3 | ± 3 | | | | ± 3 | ± 3 | | | | ± 3 | ± 3 | ± 7 | ± 7 | ± 7 |
| Visit Type[2] | cl | cl | cl | cl | ph | cl | cl | cl | cl | ph | cl | cl | cl | cl | ph | ph | cl | cl | cl | ph | ph | cl | cl | cl | cl |
| Structural MRI, safety MRI (GRE T2 star, T2 FLAIR, T2 FSE/TSE, DTI) and ASL | X | | | | | | | | | | | | | | | | | | | | | | | X | |
| Imaging of CSF space | X | | | | | | | | | | | | | | | | | | | | | | | | |
| FAQ, NPI-Q | X | X | | | | | | | | | | | | | | | | | | | | X | | X | X |
| RBANS[9] | X | X | | | | | | | | | | X | | | | | | | | | | X | | X | X |
| MMSE[9] | X | | | | | | | | | | | X | | | | | | | | | | X | | X | X |
| MHIS, CDR, GDS-SF | X | | | | | | | | | | | | | | | | | | | | | | | | |
| C-SSRS | X | X | X | | | X | X | X | X | | X | X | X | X | | | X | X | X | | | X | X | X | X |
| Serum/Plasma Biomarker Sample | | X | | | | | X | | | | | X | | | | | X | | | | | X | X | X | X |
| Thyroid Panel | X | | | | | | | | | | | | | | | | | | | | | | | | |
| PT, INR, aPTT | X | X | | | | | X | | | | | X | | | | | X | | | | | X | X | X | X |
| Archived Serum Sample[10] | | X | | | | | X | | | | | X | | | | | X | | | | | X | X | X | X |
| Drug/Alcohol Screen | X | | | | | | | | | | | | | | | | | | | | | | | | |
| ECG (12-Lead, triplicate) | X | X | | X | | | X | | | | | X | | | | | X | | | | | X | | | X |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Prior/Concomitant Therapy/Procedures | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

## Appendix A A.1. Schedule of Procedures – MAD Part 1, 4-Dose Regimen, Cohorts A and B *Continued*

| Study Period | Screen | Treatment Evaluation Period (13 Weeks) | | | | | | | | | | | | | | | | | | | | Post-Treatment Period (23 Weeks) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | -8 to -1 | 1 | | | | 2 | 5 | | | | 6 | 9 | | | | 10 | 13 | | | | 14 | 17[1] | 21 | 25 | 37 or ET[1] |
| Day | -57 to -2 | -1 | 1 | 2 | 3 | 8 | 28 | 29 | 30 | 31 | 36 | 56 | 57 | 58 | 59 | 64 | 84 | 85 | 86 | 87 | 92 | 113 | 141 | 169 | 253 |
| Visit Window (days)* | - | 0 | | | | ± 3 | ± 3 | | | | ± 3 | ± 3 | | | | ± 3 | ± 3 | | | | ± 3 | ± 3 | ± 7 | ± 7 | ± 7 |
| Visit Type[2] | cl | cl | cl | cl | ph | cl | cl | cl | cl | ph | cl | cl | cl | cl | ph | ph | cl | cl | cl | ph | ph | cl | cl | cl | cl |
| Plasma Sampling for PK | | | X[e] | X[b] | | | | X[d] | | | | | X[d] | | | | | X[f] | X[b] | | | X | X | X | X |
| Plasma Immunogenicity Testing | | | X[d] | | | | | X[d] | | | | | | | | | | X[d] | | | | X | | | X |
| Local PT, INR, aPTT, platelets[11] | X | X | | | | | X | | | | | X | | | | | X | | | | | X | X | | X[12] |
| CSF Sample for Screening Tests | X | | | | | | | | | | | | | | | | | | | | | | | | |
| CSF Sample for Biomarker Panel | X | | X[d] | | | | | X[d] | | | | | X[d] | | | | | X[d] | | | | X | X | | X[13] |
| CSF Samples for PK, Safety | | | X[d] | | | | | X[d] | | | | | X[d] | | | | | X[d] | | | | X | X | | X[13] |
| Archived CSF Sample | X | | X[d] | | | | | X[d] | | | | | X[d] | | | | | X[d] | | | | X | X | | X[13] |

## Appendix A A.2. Schedule of Procedures – MAD Part 1, 4-Dose Regimen, Cohorts C and D

| Study Period | Screen | Treatment Evaluation Period (13 Weeks) | | | | | | | | | | | | | | | | | | | | Post-Treatment Period (23 Weeks) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | -8 to -1 | 1 | | | | 2 | 5 | | | | 6 | 9 | | | | 10 | 13 | | | | 14 | 17[1] | 21 | 25 | 29 | 37 or ET[1] |
| Day | -57 to -2 | -1 | 1 | 2 | 3 | 8 | 28 | 29 | 30 | 31 | 36 | 56 | 57 | 58 | 59 | 64 | 84 | 85 | 86 | 87 | 92 | 113 | 141 | 169 | 197 | 253[15] |
| Visit Window (days)* | - | 0 | | | | ± 3 | ± 3 | | | | ± 3 | ± 3 | | | | ± 3 | ± 3 | | | | ± 3 | ± 3 | ± 7 | ± 7 | ± 7 | ± 7 |
| Visit Type[2] | cl | cl | cl | cl | ph | cl | cl | cl | cl | ph | cl | cl | cl | cl | ph | ph | cl | cl | cl | ph | ph | cl | cl | cl | cl | cl |
| Study Drug Administration | | | X | | | | | X | | | | | X | | | | | X | | | | | | | | |
| Overnight Stay[3] | | | X→ | | | | | X→ | | | | | X→ | | | | | X→ | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| Genetic Testing[4] | | X | | | | | | | | | | | | | | | | | | | | | | | | |
| International Standard Classification of Education | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| Body Weight and Height[5] | X | X | | | | | X | | | | | X | | | | | X | | | | | X | X | X | X | X |
| Physical & Neurological Exam[6] | X | | X[a] | X[b] | | X | | X[a] | X[b] | | X | | X[a] | X[b] | | | | X[a] | X[b] | | | X | X | X | X | X |
| Vital Signs (BP, HR)[7], (RR, T) | X | X | X[c] | | | | X | X[c] | | | | X | X[c] | | | | X | X[c] | | | | X | X | X | X | X |
| Orthostasis Assessment | X | | | | | | | | | | | | | | | | | | | | | | | | | X |
| HIV; Hepatitis B & C; serum folate, B12, homocysteine and uric acid, treponema | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| FSH[8] | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| Chemistry Panel | X | X | | | | | X | | | | | X | | | | | X | | | | | X | X | X | X | X |
| Hematology | X | X | | | | | X | | | | | X | | | | | X | | | | | X | X | X | X | X |
| Urinalysis | X | X | | | | | X | | | | | X | | | | | X | | | | | X | X | X | X | X |

## Appendix A A.2. Schedule of Procedures – MAD Part 1, 4-Dose Regimen, Cohorts C and D *Continued*

| Study Period | Screen | Treatment Evaluation Period (13 Weeks) | | | | | | | | | | | | | | | | | | | | Post-Treatment Period (23 Weeks) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | -8 to -1 | 1 | | | | 2 | 5 | | | | 6 | 9 | | | | 10 | 13 | | | | 14 | 17[1] | 21 | 25 | 29 | 37 or ET[1] |
| Day | -57 to -2 | -1 | 1 | 2 | 3 | 8 | 28 | 29 | 30 | 31 | 36 | 56 | 57 | 58 | 59 | 64 | 84 | 85 | 86 | 87 | 92 | 113 | 141 | 169 | 197 | 253[15] |
| Visit Window (days)* | - | 0 | | | | ± 3 | ± 3 | | | | ± 3 | ± 3 | | | | ± 3 | ± 3 | | | | ± 3 | ± 3 | ± 7 | ± 7 | ± 7 | ± 7 |
| Visit Type[2] | cl | cl | cl | cl | ph | cl | cl | cl | cl | ph | cl | cl | cl | cl | ph | ph | cl | cl | cl | ph | ph | cl | cl | cl | cl | cl |
| Structural MRI, safety MRI (GRE T2 star, T2 FLAIR, T2 FSE/TSE, DTI) and ASL | X | | | | | | | | | | | | | | | | | | | | | | | X | | |
| FDG-PET or Tau PET[14] | X | | | | | | | | | | | | | | | | | | | | | | | X | | |
| Imaging of CSF space | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| FAQ, NPI-Q | X | X | | | | | | | | | | | | | | | | | | | | X | | X | | X |
| RBANS[9] | X | X | | | | | | | | | | X | | | | | | | | | | X | | X | | X |
| MMSE[9] | X | | | | | | | | | | | X | | | | | | | | | | X | | X | | X |
| MHIS, CDR, GDS-SF | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| C-SSRS | X | X | X | | | X | X | X | X | | X | X | X | X | | | X | X | X | | | X | X | X | X | X |
| Serum/Plasma Biomarker Sample | | X | | | | | X | | | | | X | | | | | X | | | | | X | X | X | X | X |
| Thyroid Panel | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| PT, INR, aPTT | X | X | | | | | X | | | | | X | | | | | X | | | | | X | X | X | X | X |
| Archived Serum Sample[10] | | X | | | | | X | | | | | X | | | | | X | | | | | X | X | X | X | X |
| Drug/Alcohol Screen | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| ECG (12-Lead, triplicate) | X | X | | X | | | X | | | | | X | | | | | X | | | | | X | | | | X |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Prior/Concomitant Therapy/Procedures | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

## Appendix A A.2. Schedule of Procedures – MAD Part 1, 4-Dose Regimen, Cohorts C and D *Continued*

| **Study Period** | **Screen** | **Treatment Evaluation Period (13 Weeks)** | | | | | | | | | | | | | | | | | | | | **Post-Treatment Period (23 Weeks)** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Week** | **-8 to -1** | **1** | | | | **2** | **5** | | | | **6** | **9** | | | | **10** | **13** | | | | **14** | **17[1]** | **21** | **25** | **29** | **37 or ET[1]** |
| **Day** | **-57 to -2** | **-1** | **1** | **2** | **3** | **8** | **28** | **29** | **30** | **31** | **36** | **56** | **57** | **58** | **59** | **64** | **84** | **85** | **86** | **87** | **92** | **113** | **141** | **169** | **197** | **253[15]** |
| **Visit Window (days)*** | **-** | **0** | | | | **± 3** | **± 3** | | | | **± 3** | **± 3** | | | | **± 3** | **± 3** | | | | **± 3** | **± 3** | **± 7** | **± 7** | **± 7** | **± 7** |
| **Visit Type[2]** | **cl** | **cl** | **cl** | **cl** | **ph** | **cl** | **cl** | **cl** | **cl** | **ph** | **cl** | **cl** | **cl** | **cl** | **ph** | **ph** | **cl** | **cl** | **cl** | **ph** | **ph** | **cl** | **cl** | **cl** | **cl** | **cl** |
| Plasma Sampling for PK | | | X[e] | X[b] | | | | X[d] | | | | | X[d] | | | | | X[f] | X[b] | | | X | X | X | X | X |
| Plasma Immunogenicity Testing | | | X[d] | | | | | X[d] | | | | | | | | | | X[d] | | | | X | | | | X |
| Local PT, INR, aPTT, platelets[11] | X | X | | | | | X | | | | | X | | | | | X | | | | | | X | | X | X[12] |
| CSF Sample for Screening Tests | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| CSF Sample for Biomarker Panel | X | | X[d] | | | | | X[d] | | | | | X[d] | | | | | X[d] | | | | | X | | X | X[13] |
| CSF Samples for PK, Safety | | | X[d] | | | | | X[d] | | | | | X[d] | | | | | X[d] | | | | | X | | X | X[13] |
| Archived CSF Sample | X | | X[d] | | | | | X[d] | | | | | X[d] | | | | | X[d] | | | | | X | | X | X[13] |

## Appendix A A.3. Schedule of Procedures – MAD Part 1, 2-Dose Regimen, Cohort D

| Study Period | Screen | Treatment Evaluation Period (13 Weeks) | | | | | | | | | | | | Post-Treatment Period (23 Weeks) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | -8 to -1 | 1 | | | | 2 | 5 | 9 | 13 | | | | 14 | 17[1] | 21 | 25 | 29 | 37 or ET[1] |
| Day | -57 to -2 | -1 | 1 | 2 | 3 | 8 | 29 | 57 | 84 | 85 | 86 | 87 | 92 | 113 | 141 | 169 | 197 | 253[15] |
| Visit Window (days)* | - | 0 | | | | ± 3 | ± 3 | ± 3 | ± 3 | | | | ± 3 | ± 3 | ± 7 | ± 7 | ± 7 | ± 7 |
| Visit Type[2] | cl | cl | cl | cl | ph | cl | cl | cl | cl | cl | cl | ph | ph | cl | cl | cl | cl | cl |
| Study Drug Administration | | | X | | | | | | | X | | | | | | | | |
| Overnight Stay[3] | | | X→ | | | | | | | X→ | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion | X | | | | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | | | | |
| Genetic Testing[4] | | X | | | | | | | | | | | | | | | | |
| International Standard Classification of Education | X | | | | | | | | | | | | | | | | | |
| Body Weight and Height[5] | X | X | | | | | X | X | X | | | | | X | X | X | X | X |
| Physical & Neurological Exam[6] | X | | X[a] | X[b] | | X | X | X | | X[a] | X[b] | | | X | X | X | X | X |
| Vital Signs (BP, HR)[7], (RR, T) | X | X | X[c] | | | | X | X | X | X[c] | | | | X | X | X | X | X |
| Orthostasis Assessment | X | | | | | | | | | | | | | | | | | X |
| HIV; Hepatitis B & C; serum folate, B12, homocysteine and uric acid, treponema | X | | | | | | | | | | | | | | | | | |
| FSH[8] | X | | | | | | | | | | | | | | | | | |
| Chemistry Panel | X | X | | | | | X | X | X | | | | | X | X | X | X | X |
| Hematology | X | X | | | | | X | X | X | | | | | X | X | X | X | X |
| Urinalysis | X | X | | | | | X | X | X | | | | | X | X | X | X | X |

## Appendix A A.3. Schedule of Procedures – MAD Part 1, 2-Dose Regimen, Cohort D *Continued*

| Study Period | Screen | Treatment Evaluation Period (13 Weeks) | | | | | | | | | | | | Post-Treatment Period (23 Weeks) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | -8 to -1 | 1 | | | | 2 | 5 | 9 | 13 | | | | 14 | 17[1] | 21 | 25 | 29 | 37 or ET[1] |
| Day | -57 to -2 | -1 | 1 | 2 | 3 | 8 | 29 | 57 | 84 | 85 | 86 | 87 | 92 | 113 | 141 | 169 | 197 | 253[15] |
| Visit Window (days)* | - | 0 | | | | ± 3 | ± 3 | ± 3 | ± 3 | | | | ± 3 | ± 3 | ± 7 | ± 7 | ± 7 | ± 7 |
| Visit Type[2] | cl | cl | cl | cl | ph | cl | cl | cl | cl | cl | cl | ph | ph | cl | cl | cl | cl | cl |
| Structural MRI, safety MRI (GRE T2 star, T2 FLAIR, T2 FSE/TSE, DTI) and ASL | X | | | | | | | | | | | | | | | X | | |
| FDG-PET or Tau PET[14] | X | | | | | | | | | | | | | | | X | | |
| Imaging of CSF space | X | | | | | | | | | | | | | | | | | |
| FAQ, NPI-Q | X | X | | | | | | | | | | | | X | | X | | X |
| RBANS[9] | X | X | | | | | | X | | | | | | X | | X | | X |
| MMSE[9] | X | | | | | | | X | | | | | | X | | X | | X |
| MHIS, CDR, GDS-SF | X | | | | | | | | | | | | | | | | | |
| C-SSRS | X | X | X | | | X | X | X | X | X | X | | | X | X | X | X | X |
| Serum/Plasma Biomarker Sample | | X | | | | | X | X | X | | | | | X | X | X | X | X |
| Thyroid Panel | X | | | | | | | | | | | | | | | | | |
| PT, INR, aPTT | X | X | | | | | X | X | X | | | | | X | X | X | X | X |
| Archived Serum Sample[10] | | X | | | | | X | X | X | | | | | X | X | X | X | X |
| Drug/Alcohol Screen | X | | | | | | | | | | | | | | | | | |
| ECG (12-Lead, triplicate) | X | X | | X | | | X | X | X | | | | | X | | | | X |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Prior/Concomitant Therapy/Procedures | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

## Appendix A A.3. Schedule of Procedures – MAD Part 1, 2-Dose Regimen, Cohort D *Continued*

| Study Period | Screen | Treatment Evaluation Period (13 Weeks) | | | | | | | | | | | | Post-Treatment Period (23 Weeks) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | -8 to -1 | 1 | | | | 2 | 5 | 9 | 13 | | | | 14 | 17[1] | 21 | 25 | 29 | 37 or ET[1] |
| Day | -57 to -2 | -1 | 1 | 2 | 3 | 8 | 29 | 57 | 84 | 85 | 86 | 87 | 92 | 113 | 141 | 169 | 197 | 253[15] |
| Visit Window (days)* | - | 0 | | | | ± 3 | ± 3 | ± 3 | ± 3 | | | | ± 3 | ± 3 | ± 7 | ± 7 | ± 7 | ± 7 |
| Visit Type[2] | cl | cl | cl | cl | ph | cl | cl | cl | cl | cl | cl | ph | ph | cl | cl | cl | cl | cl |
| Plasma Sampling for PK | | | X[e] | X[b] | | | X | X | | X[f] | X[b] | | | X | X | X | X | X |
| Plasma Immunogenicity Testing | | | X[d] | | | | X | | | X[d] | | | | X | | | | X |
| Local PT, INR, aPTT, platelets[11] | X | X | | | | | | | X | | | | | | X | | X | X[12] |
| CSF Sample for Screening Tests | X | | | | | | | | | | | | | | | | | |
| CSF Sample for Biomarker Panel | X | | X[d] | | | | | | | X[d] | | | | | X | | X | X[13] |
| CSF Samples for PK, Safety | | | X[d] | | | | | | | X[d] | | | | | X | | X | X[13] |
| Archived CSF Sample | X | | X[d] | | | | | | | X[d] | | | | | X | | X | X[13] |

Footnotes are applicable to A.1., A.2., and A.3. Schedule of Procedures

Note: If not specifically labeled, "X" means anytime; ET = early termination

* Visit windows are calculated relative to Day 1. Note that within each block of visits associated with dose administration, the visits must occur on 4 consecutive days. Under the 4-dose regimen, there are 4 "visit blocks" in Part 1: (Days -1, 1, 2, and 3), (Days 28, 29, 30, and 31), (Days 56, 57, 58, and 59), and (Days 84, 85, 86, and 87); under the 2-dose regimen there are 2 "visit blocks" in Part 1: (Days -1, 1, 2, and 3) and (Days 84, 85, 86, and 87).

1 If the patient terminates early from the Treatment Evaluation Period but is willing to participate in the Post-Treatment Period, the patient should complete all visits in the "visit block*" associated with the visit and then proceed to the Week 17 visit approximately 4 weeks after last dose and complete all visits in the Post-Treatment Period. If the patient terminates early from the Treatment Evaluation Period and is not willing to participate in the Post-Treatment Period or if the patient terminates early from the Post-Treatment Period, the patient should complete all visits in the "visit block*" associated with the visit and then proceed to the Week 37 visit as an Early Termination Visit (approximately 4 weeks after the last dose)

2 cl = clinic visit; ph = phone visit

3 On the Day 1 dosing day, the patient must stay in the clinic overnight and undergo safety monitoring follow-up as scheduled on Day 2. On the other dosing days, the patient may either stay in the clinic overnight or be discharged, provided the patient returns to the clinic on the day after the dosing for all required assessments

## Appendix A Schedule of Procedures – MAD Part 1, all Cohorts *Continued*

4 *APP, PSEN1, PSEN2, APOE, BCHE, IL1RAP* and *MAPT H1* haplotype (unless tested previously and laboratory report is available for documentation)

5 Height measured at Screening only

6 Full physical and neurological exam (including fundi) to be given at Screening and abbreviated physical (but full neurological) exam to be given during treatment and follow-up period as indicated to assess changes from Screening. In addition to administration on the visits shown, neurological exam should be conducted if patient experiences an adverse event suggestive of cognitive or motor dysfunction

7 Measured in triplicate at the Day 1 visit (pre-dose only)

8 Women who are not surgically sterile

9 In addition to administration on the visits shown, RBANS and MMSE should be administered if the patient experiences an adverse event suggestive of cognitive or motor dysfunction

10 Stored at -80 °C for follow-up exploration of laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies) in this or subsequent clinical studies of ISIS 814907

11 Local laboratory analysis of PT, INR, aPTT, and platelets must be conducted, and results reviewed prior to performing any LP on the next day during the Treatment Evaluation Period or the same day during the Post-Treatment Period. At Screening, analysis of PT, INR, aPTT, and platelets must be conducted and results reviewed within 2 days prior to the Screening LP

12 Local analysis of PT, INR, aPTT, and platelets is only conducted at Day 253 (Week 37) in patients who will undergo CSF sampling at this visit if they missed a previous LP during the study

13 CSF sampling will be conducted at Day 253 (Week 37) as part of the ET procedures in *only* those patients who did not complete all previous CSF samplings in the study

14 Each patient will undergo PET imaging with either FDG or Tau. FDG-PET will be performed unless Tau-PET is available and has been approved at the site. As soon as Tau-PET is approved and available at a site, patients should switch to Tau-PET imaging, instead of FDG-PET imaging, for their next scan

15 This footnote is only applicable to A.2. and A.3. Schedule of Procedures: Patients in Cohorts C and D will seamlessly transition from Part 1 to Part 2. Day 253 of Part 1 will correspond to Day -1 in Part 2. All assessments listed in MAD Part 1, Day 253 and LTE Part 2, Day -1 visits must be completed at this visit; duplicative assessments only need to be done once

Time (in reference to time of Study Drug administration):

a Pre-dose and 3 hours post IT bolus injection; conduct at 6 hours post IT bolus injection if the patient will be discharged from the clinic on this day (discharge is not permitted on Day 1; discharge is permitted on the other dosing days)

b 24 hours after prior dose of Study Drug

c Pre-dose, 3 and 6 hours post IT bolus injection

d Pre-dose

e Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours post IT bolus injection

f Pre-dose, 0.5, 1, 2, 3, 4, and 5 hours post IT bolus injection

## Appendix A A.4. Schedule of Procedures – LTE Part 2, All Cohorts

| Study Period | Regis-tration[3] | Treatment Evaluation Period (48 Weeks) | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | -3 to -1 | 1 | | | | 2 | 12 | | | | 13 | 24 | | | | 25 | 36 | | | | 37 | 48 | | | | 49 |
| Day | -21 to -2 | -1[¥] | 1[+] | 2 | 3 | 8 | 84[¥] | 85 | 86 | 87 | 92 | 168[¥] | 169 | 170 | 171 | 176 | 252[¥] | 253 | 254 | 255 | 260 | 336[¥] | 337 | 338 | 339 | 344 |
| Visit Window (days)* | - | 0 | | | | ± 3 | ± 3 | | | | ± 3 | ± 3 | | | | ± 3 | ± 3 | | | | ± 3 | ± 3 | | | | ± 3 |
| Visit Type[2] | cl | cl | cl | cl | ph | cl | cl | cl | cl | ph | cl | cl | cl | cl | ph | ph | cl | cl | cl | ph | ph | cl | cl | cl | ph | ph |
| ISIS 814907 Administration | | | X | | | | | X | | | | | X | | | | | X | | | | | X | | | |
| Overnight Stay[4] | | | X→ | | | | | X→ | | | | | X→ | | | | | X→ | | | | | X→ | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| Medical History[5] | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| Body Weight | X | X | | | | | X | | | | | X | | | | | X | | | | | X | | | | |
| Physical & Neurological Exam[6] | X | | X[a] | X[b] | | X | | X[a] | X[b] | | X | | X[a] | X[b] | | | | X[a] | X[b] | | | | X[a] | X[b] | | |
| Vital Signs (BP, HR)[7], (RR, T) | X | X | X[c] | | | | X | X[c] | | | | X | X[c] | | | | X | X[c] | | | | X | X[c] | | | |
| Orthostasis Assessment | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| Chemistry Panel | X | X | | | | | X | | | | | X | | | | | X | | | | | X | | | | |
| Hematology | X | X | | | | | X | | | | | X | | | | | X | | | | | X | | | | |
| Urinalysis | X | X | | | | | X | | | | | X | | | | | X | | | | | X | | | | |
| Structural MRI, safety MRI (GRE T2 star, T2 FLAIR, T2 FSE/TSE, DTI) and ASL | X | | | | | | | | | | | | | | | | X | | | | | X[14] | | | | |
| FDG-PET or Tau PET[8] | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| FAQ, NPI-Q | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| RBANS[9] | X | | | | | | | | | | | X | | | | | | | | | | X | | | | |

## Appendix A A.4. Schedule of Procedures – LTE Part 2, All Cohorts *Continued*

| Study Period | Regis-tration[3] | Treatment Evaluation Period (48 Weeks) | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | -3 to -1 | 1 | | | | 2 | 12 | | | | 13 | 24 | | | | 25 | 36 | | | | 37 | 48 | | | | 49 |
| Day | -21 to -2 | -1[¥] | 1[+] | 2 | 3 | 8 | 84[¥] | 85 | 86 | 87 | 92 | 168[¥] | 169 | 170 | 171 | 176 | 252[¥] | 253 | 254 | 255 | 260 | 336[¥] | 337 | 338 | 339 | 344 |
| Visit Window (days)* | - | 0 | | | | ± 3 | ± 3 | | | | ± 3 | ± 3 | | | | ± 3 | ± 3 | | | | ± 3 | ± 3 | | | | ± 3 |
| Visit Type[2] | cl | cl | cl | cl | ph | cl | cl | cl | cl | ph | cl | cl | cl | cl | ph | ph | cl | cl | cl | ph | ph | cl | cl | cl | ph | ph |
| MMSE[9] | X | | | | | | | | | | | X | | | | | | | | | | X | | | | |
| MHIS, GDS-SF | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| CDR | X | | | | | | | | | | | | | | | | | | | | | | | | | |
| C-SSRS | X | X | X | | | | X | X | X | | | X | X | X | | | X | X | X | | | X | X | X | | |
| PT, INR, aPTT | | X | | | | | X | | | | | X | | | | | X | | | | | X | | | | |
| Local PT, INR, aPTT, platelets[10] | | X | | | | | X | | | | | X | | | | | X | | | | | X | | | | |
| ECG (12-Lead, triplicate) | X | X | | | | | X | | | | | X | | | | | X | | | | | | | | | |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Prior/Concomitant Therapy/Procedures | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Serum/Plasma Biomarker | | X | | | | | X | | | | | X | | | | | X | | | | | X | | | | |
| Archived serum sample[11] | | X | | | | | X | | | | | X | | | | | X | | | | | X | | | | |
| Plasma sampling for PK | | | X[e] | X[b] | | | | X[d] | | | | | X[d] | | | | | X[d] | | | | | X[f] | X[b] | | |
| Plasma Immunogenicity testing | | | X[d] | | | | | X[d] | | | | | X[d] | | | | | X[d] | | | | | X[d] | | | |
| CSF Sample for Biomarker Panel | | | X[d] | | | | | X[d] | | | | | X[d] | | | | | X[d] | | | | | X[d] | | | |
| CSF Samples for PK, Safety | | | X[d] | | | | | X[d] | | | | | X[d] | | | | | X[d] | | | | | X[d] | | | |
| Archived CSF Sample | | | X[d] | | | | | X[d] | | | | | X[d] | | | | | X[d] | | | | | X[d] | | | |

## Appendix A A.4. Schedule of Procedures – LTE Part 2, All Cohorts *Continued*

| Study Period | Post-Treatment Period (16 Weeks) | |
|---|---|---|
| **Week** | **60** | **64 or ET[1]** |
| **Day** | **421** | **449** |
| **Visit Window (days)*** | **± 3** | **± 7** |
| **Visit Type[2]** | **cl** | **cl** |
| ISIS 814907 Administration | | |
| Overnight Stay[4] | | |
| Informed Consent | | |
| Inclusion/Exclusion | | |
| Medical History[5] | | |
| Body Weight | | X |
| Physical & Neurological Exam[6] | X | X |
| Vital Signs (BP, HR)7, (RR, T) | X | X |
| Orthostasis Assessment | | X |
| Chemistry Panel | X | X |
| Hematology | X | X |
| Urinalysis | X | X |
| Structural MRI, safety MRI (GRE T2 star, T2 FLAIR, T2 FSE/TSE, DTI) and ASL | | X |
| FDG-PET or Tau PET[8] | | X |
| FAQ, NPI-Q | | X |
| RBANS[9] | | X |
| MMSE[9] | | X |
| MHIS, GDS-SF | | |
| CDR | | X |
| C-SSRS | X | X |
| PT, INR, aPTT | X | X |
| Local PT, INR, aPTT, platelets[10] | X | X[12] |

## Appendix A A.4. Schedule of Procedures – LTE Part 2, All Cohorts *Continued*

| Study Period | Post-Treatment Period (16 Weeks) | |
|---|---|---|
| **Week** | **60** | **64 or ET[1]** |
| **Day** | **421** | **449** |
| **Visit Window (days)*** | **± 3** | **± 7** |
| **Visit Type[2]** | **cl** | **cl** |
| ECG (12-Lead, triplicate) | | X |
| Adverse Events | X | X |
| Prior/Concomitant Therapy/Procedures | X | X |
| Serum/Plasma Biomarker | X | X |
| Archived serum sample[11] | X | X |
| Plasma sampling for PK | X | X |
| Plasma Immunogenicity testing | | X |
| CSF Sample for Biomarker Panel | X | X[13] |
| CSF Samples for PK, Safety | X | X[13] |
| Archived CSF Sample | X | X[13] |

Footnotes are applicable to A.4. Schedule of Procedures

Note: If not specifically labeled, "X" means anytime; ET = early termination

* Visit windows are calculated relative to Day 1. Note that within each block of visits associated with dose administration, the visits must occur on 4 consecutive days. There are 5 "visit blocks" in Part 2: (Days -1, 1, 2, and 3), (Days 84, 85, 86, and 87), (Days 168, 169, 170, and 171), (Days 252, 253, 254, and 255), and (Days 336, 337, 338, and 339).

1 If the patient terminates early from the Treatment Evaluation Period but is willing to participate in the Post-Treatment Period, the patient should complete all visits in the "visit block*" associated with the visit and then proceed to the Week 60 visit approximately 4 weeks after last dose and complete all visits in the Post-Treatment Period. If the patient terminates early from the Treatment Evaluation Period and is not willing to participate in the Post-Treatment Period or if the patient terminates early from the Post-Treatment Period, the patient should complete all visits in the "visit block*" associated with the visit and then proceed to the Week 64 visit as an Early Termination Visit (approximately 4 weeks after the last dose)

2 cl = clinic visit; ph = phone visit

3 The Registration Visit is not needed for patients who seamlessly move from Part 1 to Part 2 (i.e., patients from Cohorts C and D) as all assessments done at Registration will either be performed during the Part 1, Day 253 visit or during the Part 2, Day -1 visit

## Appendix A A.4. Schedule of Procedures – LTE Part 2, All Cohorts *Continued*

4 On the Day 1 dosing day, all patients must stay in the clinic overnight and undergo safety monitoring follow-up as scheduled on Day 2. All patients entering Part 2 must be kept at the Study Center for at least 24 hours following the first ISIS 814907 administration and undergo safety monitoring as scheduled. This 24-hour safety monitoring is required as patients in Cohorts A and B will receive a higher dose of ISIS 814907 in Part 2 than they did in Part 1. For Cohorts C and D patients who will transition to an ISIS 814907 dose in Part 2 that is the same as the dose they received in Part 1, the 24-hour monitoring is necessary as it will not be known which patients received placebo in Part 1 and are therefore receiving ISIS 814907 for the first time in Part 2. On all the other dosing days, the patient may either stay in the clinic overnight or be discharged, provided the patient returns to the clinic on the day after the dosing for all required assessments

+ **Modification due to COVID19 pandemic**; If an overnight stay cannot be conducted on Day 1, this may be converted to a 6-hour visit. The following safety measures for the shortened Day 1 LTE visit must be implemented and documented:

- Discuss with the patient changing the visit from an overnight stay to a visit that is 6-hours post-dose (i.e., so will inevitably be longer than 6 hours).
- Patient must return the next day for their Day 2 post-dose visit.
- Post-dose, the caregiver must remain in the home or hotel with the patient overnight. If patient will not reside in proximity to the site (within 1-hour travel time), there must be clear provision for timely neurological assessment and admission in the unlikely event that this is required.
- Site staff/PI must follow-up with the patient post-discharge. Please notify Ionis and Syneos of planned times the patient will be contacted post-discharge for Sponsor review and approval.
- Site staff/PI is available overnight if the patient requires medical attention via phone or in-person and provide contact information to patient. Please document who will be available from the site overnight.

5 Not needed for patients who seamlessly move from Part 1 to Part 2 (i.e., Patients from Cohorts C and D as Day 253 of Part 1 corresponds to Day -1 of Part 2)

6 Full physical and neurological exams (including fundi) to be given at Registration and abbreviated physical (but full neurological) exam to be given during treatment and follow-up period as indicated to assess changes from pre-dose exams. In addition to administration on the visits shown, neurological exam should be conducted if patient experiences an adverse event suggestive of cognitive or motor dysfunction

7 Measured in triplicate at the Day 1 visit (pre-dose only)

8 Each patient will undergo PET imaging with either FDG or Tau. FDG-PET will be performed unless Tau-PET is available and has been approved at the site. As soon as Tau-PET is approved and available at a site, patients should switch to Tau-PET imaging, instead of FDG-PET imaging, for their next scan

9 In addition to administration on the visits shown, RBANS and MMSE should be administered if the patient experiences an adverse event suggestive of cognitive or motor dysfunction

10 Local laboratory analysis of PT, INR, aPTT, and platelets must be conducted and results reviewed prior to performing any LP on the next day during the Treatment Evaluation Period or the same day during the Post-Treatment Period

11 Stored at -80 °C for follow-up exploration of laboratory findings and/or adverse events (e.g., measurement of cytokine and/or chemokine levels, measurement of additional markers of kidney function, measurement of antibodies) in this or subsequent clinical studies of ISIS 814907

12 Local analysis of PT, INR, aPTT, and platelets is only conducted at Day 449 (Week 64) in patients who will undergo CSF sampling at this visit if they missed a previous LP during the study

13 CSF sampling will be conducted at Day 449 (Week 64) as part of the ET procedures in only those patients who did not complete all previous CSF samplings in the study

14 Safety MRI will only be performed at Day 336 if the safety MRI was not performed at Day 252.

Time (in reference to time of ISIS 814907 administration):

a Pre-dose and 3 hours post IT bolus injection; conduct at 6 hours post IT bolus injection if the patient will be discharged from the clinic on this day (discharge is not permitted on Day 1; discharge is permitted on the other dosing days)
b 24 hours after prior dose of ISIS 814907
c Pre-dose, 3 and 6 hours post IT bolus injection
d Pre-dose
e Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours post IT bolus injection
f Pre-dose, 0.5, 1, 2, 3, 4, and 5 hours post IT bolus injection

¥ **Modification due to COVID19 pandemic**: The study assessments performed at the pre-dose visit can be performed the same day as the dosing visit prior to dosing. ***Local laboratory analysis of PT, INR, aPTT, and platelets must be performed, and results reviewed prior to dosing.*** This applies to the following visits: Day -1 and 1 (Cohorts A and B), Day 253 and 1 (Cohorts C and D), Day 84 and 85, Day 168 and 169, Day 252 and 253, Day 336 and 337. If allowed per local guidance and it is safe to do so, patients should return for their post-dose clinic visit as planned on Days 2, 86, 170, 254, and 338.

# Appendix B List of Laboratory Analytes

## Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to characterize the profile of ISIS 814907 or other similar oligonucleotides.

**Clinical Chemistry**
Sodium
Potassium
Chloride
Total protein
Albumin
Calcium
Magnesium
Phosphorus
Bicarbonate
Glucose
BUN
Creatinine
Total serum Bilirubin
Uric acid
Alkaline phosphatase
AST (SGOT)
ALT (SGPT)
GGT
CPK

**Hematology**
Red blood cells
Hemoglobin
Hematocrit
Platelets
MCV, MCH, MCHC
White blood cells (WBC)
WBC Differential (% and absolute)
- Neutrophils
- Eosinophils
- Basophils
- Lymphocytes
- Monocytes

**Urinalysis**
Specific gravity
pH
Protein
P/C ratio
Glucose
Ketones
Urobilinogen
Leukocyte esterase
Nitrite
Bilirubin
Blood
Red blood cells
WBC
Epithelial cells
Bacteria
Casts
Crystals
Color
Appearance

**Thyroid Panel**
TSH
Free T4
Free T3

**Coagulation**
aPTT
PT
INR

**Screening Tests (Plasma/Serum)**
Hepatitis B surface antigen
Hepatitis C antibody
HIV antibody
FSH (women only)
Drug/Alcohol screen[2]
Serum folate
Serum B12
Serum homocysteine
Serum uric acid
Treponemal antibody

**Screening Tests (CSF)**
Aβ
total tau
p-tau

**Genetics**
*APOE*
*BCHE*
*IL1RAP*
*H1 MAPT haplotype*
*APP*
*PSEN1*
*PSEN2*

**PK[1]**
Plasma and CSF
ISIS 814907 levels

**CSF Safety Panel (Minimum Requirements)**
Red blood cells
WBC
Glucose
Protein
Albumin

**Exploratory CSF Biomarker Panel**
Clusterin
FH
C3
IL-6
TNFα
IL-1β
MCP-1
YKL-40
sTREM2
VILIP1
ApoE
BCHE
Chromogranin B
Neurogranin
SNAP25
S100B
Aβ
total tau
p-tau
Neurofilament light chain
Homocysteine (Screening and Day 1 only)
B12 (Screening and Day 1 only)
Folate (Screening and Day 1 only)

**Serum/Plasma Biomarker Panel**
24S-hydroxycholesterol
Neurofilament light chain
Tau
IL-6
TNFα

**Additional Safety Tests (plasma)**
Immunogenicity[1]

1 Any of the collected PK or immunogenicity plasma, CSF or urine samples from the study patients may also be used by Ionis for investigation of possible biomarkers of disease or the PD effects of ISIS 814907 or for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, immunogenicity assessments (including assay development and validation purposes) or to assess other actions of ISIS 814907 with plasma, CSF or urine constituents. Also, if a relationship between genetic markers and disease progression becomes apparent during the study or within 5 years after the end of the study, the genetic markers may be identified in archived samples for investigation of association with drug effect

2 Amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, ethanol, opiates

# Appendix C PK Sampling Schedule

## Appendix C PK Sampling Schedule – MAD Part 1, 4-Dose Regimen (Cohorts A and B)

| Study Period | Treatment Evaluation Period (13 Weeks) | | | | | | Post-Treatment Period or Early Termination Visit (23 Weeks) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Week | 1 | | 5 | 9 | 13 | | 17 | 21 | 25 | 37 or ET |
| Day | 1 | 2 | 29 | 57 | 85 | 86 | 113 | 141 | 169 | 253 |
| CSF Sampling | Pre-dose | | Pre-dose | Pre-dose | Pre-dose | | Anytime | Anytime | | Anytime[1] |
| Plasma Sampling | Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8,12 hours post IT bolus injection | 24 hours post Day 1 IT bolus injection | Pre-dose | Pre-dose | Pre-dose, 0.5, 1, 2, 3, 4, 5 hours post IT bolus injection | 24 hours post Day 85 IT bolus injection | Anytime | Anytime | Anytime | Anytime |

1 CSF sampling will be conducted at Day 253 (Week 37) as part of the ET procedures in only those patients who did not complete all previous CSF samplings in the study

## PK Sampling Schedule – MAD Part 1, 4-Dose Regimen (Cohorts C and D)

| Study Period | Treatment Evaluation Period (13 Weeks) | | | | | | Post-Treatment Period or Early Termination Visit (23 Weeks) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | 1 | | 5 | 9 | 13 | | 17 | 21 | 25 | 29 | 37 or ET |
| Day | 1 | 2 | 29 | 57 | 85 | 86 | 113 | 141 | 169 | 197 | 253 |
| CSF Sampling | Pre-dose | | Pre-dose | Pre-dose | Pre-dose | | | Anytime | | Anytime | Anytime[1] |
| Plasma Sampling | Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8,12 hours post IT bolus injection | 24 hours post Day 1 IT bolus injection | Pre-dose | Pre-dose | Pre-dose, 0.5, 1, 2, 3, 4, 5 hours post IT bolus injection | 24 hours post Day 85 IT bolus injection | Anytime | Anytime | Anytime | Anytime | Anytime |

1 CSF sampling will be conducted at Day 253 (Week 37) as part of the ET procedures in only those patients who did not complete all previous CSF samplings in the study

## PK Sampling Schedule – MAD Part 1, 2-Dose Regimen (Cohort D)

| Study Period | Treatment Evaluation Period (13 Weeks) | | | | | | Post-Treatment Period or Early Termination Visit (23 Weeks) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Week | 1 | | 5 | 9 | 13 | | 17 | 21 | 25 | 29 | 37 or ET |
| Day | 1 | 2 | 29 | 57 | 85 | 86 | 113 | 141 | 169 | 197 | 253 |
| CSF Sampling | Pre-dose | | | | Pre-dose | | | Anytime | | Anytime | Anytime[1] |
| Plasma Sampling | Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8,12 hours post IT bolus injection | 24 hours post Day 1 IT bolus injection | Anytime | Anytime | Pre-dose, 0.5, 1, 2, 3, 4, 5 hours post IT bolus injection | 24 hours post Day 85 IT bolus injection | Anytime | Anytime | Anytime | Anytime | Anytime |

1 CSF sampling will be conducted at Day 253 (Week 37) as part of the ET procedures in only those patients who did not complete all previous CSF samplings in the study

## PK Sampling Schedule – LTE Part 2, All Cohorts

| Study Period | Treatment Evaluation Period (48 Weeks) | | | | | | | Post-Treatment Period or Early Termination Visit (16 Weeks) | |
|---|---|---|---|---|---|---|---|---|---|
| Week | 1 | | 12 | 24 | 36 | 48 | | 60 | 64 or ET |
| Day | 1 | 2 | 85 | 169 | 253 | 337 | 338 | 421 | 449 |
| CSF Sampling | Pre-dose | | Pre-dose | Pre-dose | Pre-dose | Pre-dose | | Anytime[x] | Anytime[1x] |
| Plasma Sampling | Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 8,12 hours post IT bolus injection | 24 hours post Day 1 IT bolus injection | Pre-dose | Pre-dose | Pre-dose | Pre-dose, 0.5, 1, 2, 3, 4, 5 hours post IT bolus injection | 24 hours post Day 337 IT bolus injection | Anytime[x] | Anytime[x] |

1 CSF sampling will be conducted at Day 449 (Week 64) as part of the ET procedures in *only* those patients who did not complete all previous CSF samplings in the study

**X; Modifications due to COVID-19 pandemic:** If a visit cannot be conducted at the clinic, CSF and plasma samples for PK will not be collected

# Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

## Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to lab test abnormalities are based upon the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010.

| Adverse Event | Mild | Moderate | Severe |
|---|---|---|---|
| **Hematology** | | | |
| aPTT prolonged | >ULN - 1.5 x ULN | >1.5 - 2.5 x ULN | >2.5 x ULN; hemorrhage |
| Eosinophils increased[r] | 650 – 1,500 cell/$mm^3$ | 1,501 - 5,000 cell/$mm^3$ | >5,000 cell/$mm^3$ |
| Fibrinogen decreased | <1.0 - 0.75 x LLN or <25% decrease from baseline | <0.75 - 0.5 x LLN or 25 - <50% decrease from baseline | <0.5 x LLN or ≥50% decrease from baseline |
| Hemoglobin decreased (Anemia) | Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L | Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L | Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated |
| Hemoglobin increased | Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN | Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN | Increase in >4 g/dL above ULN or above baseline if baseline is above ULN |
| INR increased | >1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation | >1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation | >2.5 x ULN; >2.5 times above baseline if on anticoagulation |
| Lymphocyte count decreased | <LLN - 800/$mm^3$; <LLN - 0.8 x $10^9$/L | <800 - 500/$mm^3$; <0.8 - 0.5 x $10^9$ /L | <500 /$mm^3$; <0.5 x $10^9$ /L |
| Lymphocyte count increased | - | >4000/$mm^3$ - 20,000/$mm^3$ | >20,000/$mm^3$ |
| Neutrophil count decreased | <LLN - 1500/$mm^3$; <LLN - 1.5 x $10^9$ /L | <1500 - 1000/$mm^3$; <1.5 - 1.0 x $10^9$ /L | <1000/$mm^3$; <1.0 x $10^9$ /L |
| Platelet count decreased | <LLN - 75,000/$mm^3$; <LLN - 75.0 x $10^9$ /L | <75,000 - 50,000/$mm^3$; <75.0 - 50.0 x $10^9$ /L | <50,000/$mm^3$; <50.0 x $10^9$ /L |
| White blood cell decreased | <LLN - 3000/$mm^3$; <LLN - 3.0 x $10^9$ /L | <3000 - 2000/$mm^3$; <3.0 - 2.0 x $10^9$ /L | <2000/$mm^3$; <2.0 x $10^9$ /L |
| **Chemistry** | | | |
| Acidosis | pH <normal, but >=7.3 | - | pH <7.3 |
| Alanine aminotransferase increased | >ULN - 3.0 x ULN | >3.0 - 5.0 x ULN | >5.0 x ULN |
| Alkaline phosphatase increased | >ULN - 2.5 x ULN | >2.5 - 5.0 x ULN | >5.0 x ULN |
| Alkalosis | pH >normal, but ≤7.5 | - | pH >7.5 |
| Aspartate aminotransferase increased | >ULN - 3.0 x ULN | >3.0 - 5.0 x ULN | >5.0 x ULN |
| Blood bilirubin increased | >ULN - 1.5 x ULN | >1.5 - 3.0 x ULN | >3.0 x ULN |
| Cardiac troponin I increased | Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer | - | Levels consistent with myocardial infarction as defined by the manufacturer |

## Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

| Adverse Event | Mild | Moderate | Severe |
|---|---|---|---|
| Cardiac troponin T increased | Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer | - | Levels consistent with myocardial infarction as defined by the manufacturer |
| CD4 lymphocytes decreased | <LLN - 500/$mm^3$; <LLN - 0.5 x $10^9$ /L | <500 - 200/$mm^3$; <0.5 - 0.2 x $10^9$ /L | <200/$mm^3$; <0.2 x $10^9$ /L |
| CPK increased* | >ULN - <6 ULN | 6 - 10 x ULN | >10 x ULN |
| Creatinine increased | >1 - 1.5 x baseline; >ULN - 1.5 x ULN | >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN | >3.0 x baseline; >3.0 x ULN |
| GGT increased | >ULN - 2.5 x ULN | >2.5 - 5.0 x ULN | >5.0 x ULN |
| Hypercalcemia | Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L | Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic | Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated |
| Hyperglycemia | Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L | Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L | >250 mg/dL; >13.9 mmol/L; hospitalization indicated |
| Hyperkalemia | >ULN - 5.5 mmol/L | >5.5 - 6.0 mmol/L | >6.0; hospitalization indicated |
| Hypermagnesemia | >ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L | - | >3.0 mg/dL; >1.23 mmol/L |
| Hypernatremia | >ULN - 150 mmol/L | >150 - 155 mmol/L | >155 mmol/L; hospitalization indicated |
| Hyperuricemia | >ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences | - | >ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences |
| Hypoalbuminemia | <LLN - 3 g/dL; <LLN - 30 g/L | <3 - 2 g/dL; <30 - 20 g/L | <2 g/dL; <20 g/L |
| Hypocalcemia | Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L | Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic | Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated |
| Hypoglycemia | <LLN - 55 mg/dL; <LLN - 3.0 mmol/L | <55 mg/dL; <3.0 mmol/L | <40 mg/dL (<2.2 mmol/L) AND requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions‡ |
| Hypokalemia | <LLN - 3.0 mmol/L | <LLN - 3.0 mmol/L; symptomatic; intervention indicated | <3.0 mmol/L; hospitalization indicated |
| Hypomagnesemia | <LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L | <1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L | <0.9 mg/dL; <0.4 mmol/L |
| Hyponatremia | <LLN - 130 mmol/L | - | <130 mmol/L |
| Hypophosphatemia | <LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L | <2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L | <2.0 mg/dL; <0.6 mmol/L |
| Lipase increased | >ULN - 1.5 x ULN | >1.5 - 2.0 x ULN | >2.0 x ULN |
| Serum amylase increased | >ULN - 1.5 x ULN | >1.5 - 2.0 x ULN | >2.0 x ULN |

## Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities *Continued*

| Adverse Event | Mild | Moderate | Severe |
|---|---|---|---|
| **Urine** | | | |
| Proteinuria | Trace | 1+ | ≥ 2+ |
| Hematuria | 1 - 10 cells per high power field | 11 – 50 cells per high power field | > 50 cells per high power field |

*Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

†Grading for this parameter is derived from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010

‡Modified for consistency with the ADA and Endocrine Society Guidelines (Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. Diabetes Care 2013;36:1384-95)

# Protocol

| | |
|---|---|
| Version: | 1 |
| Version Date: | 11 Aug 2020 |
| Title: | 814907 CS1 Amendment 6 A Randomized, DB, Placebo-Controlled Study, Followed by an OLE, to Evaluate the Safety, Tolerability, PK and PD of Multiple Ascending Doses of Intrathecally Administered ISIS 814907 in Patients with Mild Alzheimer's |

**APPROVALS:**

| |
|---|
| [redacted] |

# Statistical Analysis Plan

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## ISIS 814907–CS1

## A Randomized, Double-Blind, Placebo-Controlled Study, Followed by an Open-Label Extension, to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 814907 in Patients with Mild Alzheimer's Disease

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**Date: 25 April 2022**

**Version: 2.0**

**Statistical Analysis Plan Signature Page**

**Ionis Pharmaceuticals, Inc.**
**2855 Gazelle Court Carlsbad, CA 92010**

Compound Name: 814907

Protocol: ISIS 814907-CS1

Study Title: A Randomized, Double-Blind, Placebo-Controlled Study, Followed by an Open-Label Extension, to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Doses of Intrathecally Administered ISIS 814907 in Patients with Mild Alzheimer's Disease

Issue Date: 7 August 2020 (Protocol Amendment 6 - ROW)
7 August 2020 (Protocol Amendment 6 - Germany)
7 August 2020 (Protocol Amendment 8 – United Kingdom)

Signature: see electronic signature and date attached to the end

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Signature: see electronic signature and date attached to the end

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# ABBREVIATION

| Abbreviation | Definition |
|---|---|
| AD | Alzheimer's disease |
| AE | Adverse event |
| ALT | Alanine aminotransferase (SGPT) |
| aPTT | Activated partial thromboplastin time |
| ARWMC | Age-Related White Matter Changes |
| ASO | Antisense oligonucleotide |
| AST | Aspartate aminotransferase (SGOT) |
| AUC | Area under the curve |
| BP | Blood pressure |
| BUN | Blood urea nitrogen |
| CDR | Clinical Dementia Rating |
| CRF | Case Report Form |
| CSF | Cerebrospinal fluid |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| CV | Coefficient of variation |
| DTI | Diffusion Tensor imaging |
| ECG | Electrocardiogram |
| FAQ | Functional Assessment Questionnaire |
| FLAIR | Fluid-attenuated inversion recovery |
| FSE | Fast spin echo |
| FSMG | Formal Safety Monitoring Group |
| GDS | Geriatric Depression Rating Scale |
| GRE | Gradient echo |
| HR | Heart rate |
| LP | Lumbar puncture |
| LTE | Long-term extension |
| MAD | Multiple ascending dose |
| MCH | Mean corpuscular hemoglobin |
| MCHC | Mean corpuscular hemoglobin concentration |
| MCV | Mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHIS | Modified Hachinski Ischemic Scale |
| MMSE | Mini-Mental State Examination |
| MRI | Magnetic resonance imaging |
| FSMG | Formal Safety Monitoring Group |
| INR | International normalized ratio |
| ISIS 814907 | Antisense inhibitor of *MAPT* |
| IT | Intrathecal(ly) |
| ITT | Intent To Treat |
| mRNA | Messenger ribonucleic acid |
| NPI-Q | Neuropsychiatric Inventory Questionnaire |
| PET | Positron emission tomography |
| PD | Pharmacodynamic(s) |

| | |
|---|---|
| PK | Pharmacokinetic(s) |
| PT | Prothrombin time |
| QTcF | QT time corrected using the Friderica's method |
| QTcB | QT time using the Bazett's method |
| RBANS | Repeatable Battery for the Assessment of Neuropsychological Status |
| ROI | Region of interest |
| RR | Respiration rate |
| SAE | Serious adverse event |
| SBP | Systolic blood pressure |
| TEAE | Treatment-emergent adverse event |
| TSE | Turbo spin echo |
| WBC | White blood cell |
| WHO-DD | World Health Organization - Drug Dictionary |

# 1. INTRODUCTION

This document provides a description of the study organization, study procedures, and the plan for the statistical analysis of the study data. Section 1 discusses study design, objectives, and endpoints; Section 2 provides the study procedures; Section 3 provides the detailed plan for the statistical analyses.

As with any statistical analysis plan (SAP), the proposed methods and approaches to the data analysis should be reviewed as flexible. The statistical analysis to some degree is iterative since so much of the planning is based on statistical and other assumptions, which require verification.

## 1.1 Study Overview

This is a Phase 1, multi-center, double-blind, randomized, placebo-controlled study of multiple IT bolus administrations of ISIS 814907 in patients with mild Alzheimer's Disease (AD) aged 50-74 years, inclusive.

This study is divided into 2 parts:

- Part 1: a randomized, double-blind, placebo-controlled multiple ascending dose (MAD) part, comprising a Screening Period of 8 weeks, a Treatment Evaluation Period of 13 weeks, and a Post-Treatment Period of 23 weeks
- Part 2: an open-label, long-term extension (LTE) part, comprising a Registration Period of 3 weeks (only for those who cannot transition seamlessly, i.e., patients from Cohorts A and B), a Treatment Evaluation Period of 48 weeks, and a Post-Treatment Period of 16 weeks (except in the UK (Amendment 7) where the Post-Treatment Period is 23 weeks)
    - For patients participating in Cohorts A and B there will be a variable gap of time between the end of Part 1 and entry into Part 2
    - Patients participating in Cohorts C and D will seamlessly transition from Part 1 to Part 2. Day 253 in Part 1 (i.e., last visit of Part 1 Post-Treatment Period) will correspond to Day -1 in Part 2 (i.e., first visit of Part 2 Treatment Evaluation Period).

***Multiple Ascending Dose, Part 1***

Four (4) ascending dose level cohorts (A, B, C, and D) of patients were enrolled sequentially and randomized with an overall ratio of 3:1 to receive ISIS 814907 or placebo. A sentinel dosing strategy was implemented. The first 2 patients at a given dose level were assigned 1:1 active: placebo, and at least 1 week elapsed between initiation of treatment in these 2 patients and initiation of treatment in additional patients at this dose level. The remaining patients were assigned to active or placebo at a 5:1 ratio for cohorts with N = 8, 8:2 ratio for cohorts with N = 12, or 11:3 ratio for cohorts with N = 16 to ensure a 3:1 active: placebo balance in each cohort. Based on the profile of effects observed in non-human primate toxicology studies, 24 hours is expected to be a sufficiently long observation period to identify possible safety

issues. Thus, as a safety measure, the sentinel dosing algorithm utilized for this study required that 1-week elapsed between initiation of treatment in the first 2 patients and initiation of treatment in subsequent patients in the cohort. Identified and potential risks associated with ISIS 814907 are described in detail in the Investigator's Brochure.

Initiation of dosing in a new cohort began after 3 conditions had been met: (1) all patients in the lower-dose cohorts have been enrolled, (2) at least 2/3 of the patients in the lower-dose cohort had been followed for at least 7 days after receipt of the fourth dose of Study Drug, and (3) a review of data (safety, PK, and PD data) collected in the lower-dose cohorts had been conducted by the Formal Safety Monitoring Group (FSMG) and a decision had been made to proceed with the next cohort.

Each patient in cohorts A, B and C received 4 doses of Study Drug with a 28-day interval between doses. In cohort D, the protocol prespecified 2 dosing regimen options: 1) four doses of Study Drug at 90 mg with a 28-day interval between doses or 2) two doses of Study Drug at 115 mg with an 84-day interval between doses. The FSMG selected the 115 mg x 2 dosing regimen. The planned dose regimens for the study are shown below. Based on emerging safety data from this study, the protocol permitted one or more cohorts to expand and enroll additional patients. PK and PD measures were collected at each dose level and compared to the results predicted by models constructed from preclinical data.

Cohort A: N = 8, mild AD, 10 mg ISIS 814907 or placebo × 4 doses
Cohort B: N = 8, mild AD, 30 mg ISIS 814907 or placebo × 4 doses
Cohort C: N = 12, mild AD, 60 mg ISIS 814907 or placebo × 4 doses
Cohort D: N = 16, mild AD, 90 mg ISIS 814907 or placebo × 4 doses *or* 115 mg ISIS 814907 or placebo × 2 doses

Following the 3-month Treatment Period, there was a 6-month Post-Treatment Period.

***Long-Term Extension, Part 2***

The ability for participants completing the MAD, Part 1, of the study to enter an open-label LTE, Part 2, of the study started with Cohort C. All patients in Cohorts C and D could seamlessly transition from Part 1 to Part 2. For patients in Cohorts C and D, Day 253 in Part 1 corresponded to Day -1 in Part 2. In Part 2, the Treatment Evaluation Period of 48 weeks was followed by a Post-Treatment Period of 16 weeks, except in the UK (Amendment 7) where the Post-Treatment Period was 23 weeks.

All patients will receive ISIS 814907 in Part 2 and will be dosed at an 84-day interval, regardless of the dose interval utilized in Part 1.

- Cohort C patients will continue the Cohort C dose (60 mg) with a quarterly (84-day) dose interval in the LTE, Part 2
- Cohort D patients will continue the Cohort D dose (115 mg) with a quarterly (84-day) dose interval in the LTE, Part 2.

- Cohort A and B patients who have completed the Treatment Evaluation and Post-Treatment Periods in Part 1 are also eligible to enter Part 2 of the study. For Cohorts A and B patients there will be a variable gap of time between the end of Part 1 and entry into Part 2. All Cohort A and B patients participating in the Part 2 LTE should be enrolled in Part 2 prior to the last patient in Cohort D entering Part 2 of the study. Cohorts A and B patients will receive the same dose as Cohort C patients (60 mg quarterly (84-day) doses).

Patients entering the LTE Part 2 will remain on the dose received when they initiate Part 2 unless ongoing review of the safety, PK/PD profile by the FSMG and the Sponsor require dose adjustments in individuals or for the entire study. The Treatment Evaluation Period of 48 weeks will be followed by a Post-Treatment Period of 16 weeks, except in the UK (Amendment 7) where the Post-Treatment Period is 23 weeks.

## 1.2 Objectives

### *1.2.1 Primary Objectives*

To evaluate the safety and tolerability of ascending dose-levels of multiple intrathecal (IT) bolus administrations of ISIS 814907, an antisense inhibitor of *MAPT* messenger ribonucleic acid (mRNA) that encodes the tau protein, in patients with AD pathology.

### *1.2.2 Secondary Objective*

To characterize the cerebrospinal fluid (CSF) pharmacokinetics (PK) of ascending dose-levels of multiple IT bolus administrations of ISIS 814907.

### *1.2.3 Exploratory Objectives*

To explore effects of multiple doses of ISIS 814907 on potential target engagement and disease progression biomarkers and clinical endpoints relevant to AD. Plasma PK properties of ISIS 814907 will also be assessed. Evaluation of CSF total tau is key exploratory endpoint. If CSF total tau protein level, and/or CSF phospho-tau protein level, are reflective of target engagement, exploratory analyses will be conducted to characterize the relationships between dose, CSF PK, and CSF total tau and CSF phospho-tau protein levels. Disease progression clinical and biological markers are included primarily as a safety measure to document any marked worsening. A lesser objective is to gain experience with these measures in an ISIS 814907 clinical study as preparation for subsequent, longer-term clinical studies. It is not expected that the majority of biomarkers and clinical measures will be impacted significantly by the 3 months of ISIS 814907 administration planned for Part 1; however, the longer-term treatment with ISIS 814907 in Part 2 may affect both biomarkers and clinical measures.

## 1.3 Endpoints

There is no single primary endpoint for assessment of safety and tolerability, the primary objective of this study. This and other important endpoints are identified in the following sections.

### *1.3.1 Safety and Tolerability Endpoints*

- Physical examination and standard neurological assessment (including fundi)
- Vital signs (Heart Rate [HR], Blood Pressure [BP], orthostatic changes, weight, respiratory rate, body temperature)
- Electrocardiograms (ECG)
- AEs and concomitant medications
- Columbia Suicide Severity Rating Scale (C-SSRS)
- CSF safety labs (cell counts, protein, albumin, glucose)
- Plasma laboratory tests (clinical chemistry, hematology)
- Urinalysis
- Safety MRI sequences (GRE T2 star, T2 FLAIR, T2 FSE/TSE, DTI)

Clinical evaluations (Section 3.7.3) and volumetric neuroimaging measures (Section 3.7.2.1) will be evaluated to monitor for unexpected deterioration.

### *1.3.2 Pharmacokinetic Endpoints*

CSF samples are collected pre-dose on each injection day during the treatment period:

- Part 1: Days 1, 29, 57, and 85 for the 4-dose regimen, or Days 1 and 85 for the 2-dose regimen.
- Part 2: Days 1, 85, 169, 253, 337.

CSF samples are also collected during the Post-Treatment Period:

- Part 1: Days 113 and 141 for patients in Cohorts A and B, and Days 141 and 197 for patients in Cohorts C and D
- Part 2: Day 421

Plasma samples will be collected for PK analyses on the following days:

**Part 1**: Days 1, 2, 29, 57, 85, and 86, during the Treatment Evaluation Period and on Days 113, 141, 169, 197 (patients in Cohorts C and D only) and 253 during the Post-Treatment Period

**Part 2**: Days 1, 2, 85, 169, 253, 337, and 338 during the Treatment Evaluation Period and on Days 421 and 449 during the Post-Treatment Period

Plasma post-distribution drug levels will be measured. $C_{max}$ and area under the curve (AUC) will be determined, and elimination half-life will be assessed where appropriate.

### *1.3.3 Exploratory Endpoints*

All endpoints in the study, including the exploratory endpoints serve as safety measures. While the below endpoints will be monitored for evidence of target engagement or PD effect, they will also be monitored to ensure the patient does not experience unexpected worsening during the study.

- Key exploratory endpoints
  - CSF total tau
    - Biochemical
  - Other potential CSF biomarkers may include, but are not limited to, target engagement (phospho-tau), A-beta42, A-beta40, neuronal injury markers (neurofilament light chain [NfL], phospho neurofilament heavy [pNfH], neuronal pentraxin, alpha-synuclein, visinin-like protein 1 [VILIP1]), synaptic markers (neurogranin [Ng], chromogranin B, synaptosomal-associated protein 25 [SNAP25]), innate immune activation markers (interleukin-6 [IL-6], tumor necrosis factor alpha [TNFα], interleukin-1 beta [IL-1β], monocyte chemoattractant protein-1 [MCP-1], S100B, chitinase-3-like protein 1 [YKL-40], complement [C3, factor H]), apolipoprotein E, clusterin, butyrylcholinesterase (BCHE), Potential blood/plasma biomarkers may include, but are not limited to NfL, pNfH, tau, IL-6, TNFα, 24S-hydroxycholesterol and uric acid
  - Neuroimaging
    - Structural MRI – Volumetric Analysis
      - Hippocampal, whole brain, intracranial and ventricle volumes
  - Exploratory MRI Analyses
    - Perfusion analysis – arterial spin labelling (ASL)
    - Diffusion analysis
    - Cortical thickness
    - White matter lesion analysis
    - CSF space analysis
  - PET (Cohorts C and D only in Part 1, and all patients in Part 2)
- Clinical Evaluations
  - Functioning/ability to perform activities of daily living
    - Functional Activities Questionnaire (FAQ)

- Cognitive
  - Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)
  - Mini-mental state examination (MMSE)
  - Clinical Dementia Rating (CDR) Scale
- Neuropsychiatric
  - Neuropsychiatric Inventory - Questionnaire (NPI-Q)

Analyses may explore relationship between selected parameters (at baseline and their progression during the study) and genetic causes of AD (*APP, PSEN1, PSEN2*), potential genetic modifiers of disease phenotype (commonly occurring risk-associated SNPs of *APOE*, *BCHE*, *IL1RAP, CD33* and *MAPT H1* haplotype).

# 2. PROCEDURES

## 2.1 General Overview of Procedures

Ionis Pharmaceuticals, Inc. (or designee) will review all study data including source documents, CRFs, and laboratory reports. The study site will enter subject source data into the case report form. Safety laboratory data will be transferred electronically from Covance Central Laboratory Services, Inc. and Medpace Reference Laboratories to Ionis Pharmaceuticals, Inc. ECG data will be transferred electronically from BioClinica, Inc. to Ionis Pharmaceuticals, Inc. Cognitive and Neuropsychiatric scale data will be transferred electronically from MedAvante, Inc. to Ionis Pharmaceuticals, Inc. The exploratory image analysis data will be transferred electronically from Invicro, a Konica Minolta Company to Ionis Pharmaceuticals, Inc. The exploratory biomarker data will be transferred electronically from both Covance Central Laboratory Services, Inc. and Immunologix Laboratories to Ionis Pharmaceuticals, Inc.

## 2.2 Randomization & Treatment Allocation

In the MAD, Part 1, of the study, a patient will be randomized after all Screening assessments have been completed and after the Investigator has verified that the patient is eligible per criteria. No patient may begin treatment prior to randomization and assignment of a unique patient identification number.

Eligible patients will be randomized centrally by an automated system to receive ISIS 814907 or placebo. Within each cohort, randomization will be 3:1 ISIS 814907: placebo as outlined in Section 1.1.

The Sponsor or designee will prepare the randomization list.

In the LTE, Part 2, of the study, patients in Cohorts A and B will be registered after all Registration visit assessments for Part 2 have been completed and the Investigator has verified that the patient is eligible per criteria. Patients in Cohort C and D will transition seamlessly based

on the Part 1 eligibility criteria and do not need to be reassessed prior to the start of Part 2. In the LTE, Part 2, all eligible patients will be enrolled by an automated system to receive ISIS 814907. Patients will retain their patient identification number assigned in Part 1.

## 2.3 Conduct

The study will be conducted in accordance with current Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) guidelines, the World Medical Association Declaration of Helsinki guidelines, the Food and Drug Administration (FDA) Code of Federal Regulations, and all other local regulatory requirements.

## 2.4 Data Monitoring

### *2.4.1 Safety Data Monitoring*

Ionis Pharmaceuticals, Inc. (or designee) is responsible for processing all reported adverse events (AEs). All serious adverse events (SAEs), reported to Ionis Pharmaceuticals, Inc. (or designee), are reviewed per standard operating procedures. The medical monitor will review all AEs and SAEs on an ongoing basis throughout the study. Ionis Pharmaceuticals, Inc. (or designee) will prepare and submit safety reports to the health authorities worldwide in accordance with local requirements. If it becomes necessary to communicate new safety information, Ionis Pharmaceuticals, Inc. (or designee) will also prepare a safety notification letter and transmit it to the study sites.

## 2.5 Data Management

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this Study.

### *2.5.1 Case Report Form (CRF) Data*

BioClinica (or designee) is responsible for creating the Electronic Data Capture (EDC) data entry screens, database and edit checks using definitions developed by Ionis Pharmaceuticals, Inc. Trennic Data Services has been contracted by Ionis Pharmaceuticals, Inc. and is responsible for the review, data management querying and locking of the database.

Data are single-entered into the EDC system by the clinical site staff. Programmed edit checks (computer logic that checks the validity of the data entered and prompts for missing data that is expected to be entered) are run and automatic queries are generated. Trennic Data Services reviews all data for accuracy and validity and generates additional queries in the EDC system when necessary. The data are corrected or an explanation concerning the query is provided in the EDC system. After all data are entered, reviewed (by Data Management and Clinical Development) and queried, and all queries resolved, the database is locked.

#### *2.5.2 Laboratory Data*

Ionis Pharmaceuticals, Inc. is responsible for the format of the laboratory electronic data transfers, transfer schedule and review of the clinical laboratory data. The safety laboratory data will be provided by Covance Central Laboratory Services, Inc. and Medpace Reference Laboratories, and stored as SAS data sets or Excel files. The exploratory CSF biomarker data will be transferred electronically from both Covance Central Laboratory Services, Inc. and Immunologix Laboratories to Ionis Pharmaceuticals, Inc. Data will be provided as SAS datasets.

#### *2.5.3 Pharmacokinetics (PK) Data*

Ionis Pharmaceuticals, Inc. is responsible for the management and review of the plasma, urine drug concentration data. This process involves reviewing the patient and visit identifiers (i.e., patient demographics) with the clinical data collected in the EDC system. The PK data are not stored in the EDC system.

#### *2.5.4 Cognitive and Neuropsychiatric Data*

MedAvante (or designee) is responsible for collecting and providing external cognitive and neuropsychiatric scale data to Ionis Pharmaceuticals, Inc. External scale datasets include Geriatric Depression Rating Scale (GDS) dataset, Modified Hachinski Ischemic Scale (MHIS) dataset, Mini-Mental State Examination (MMSE) dataset, Clinical Dementia Rating (CDR) dataset, Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) dataset, Neuropsychiatric Inventory Questionnaire (NPI-Q) dataset, Functional Assessment Questionnaire (FAQ) dataset, Columbia Suicide Severity Rating Scale (C-SSRS) dataset. Data will be provided as SAS datasets provided via SAS transport files.

#### *2.5.5 Exploratory Neuroimaging Data*

Invicro (or designee) is responsible for transferring the exploratory image analysis data to Ionis Pharmaceuticals, Inc. The datasets include volumetric MRI analysis dataset, FDG-PET and Tau-PET quantitative analysis dataset, cortical thickness analysis dataset, white matter lesion volume analysis dataset, CSF space analysis dataset, diffusion analysis dataset and perfusion analysis dataset. The final file structure will be comma separated value (.csv) files.

# 3. ANALYTICAL PLAN

## 3.1 General Overview of Analyses

Descriptive summary statistics including number of patients, mean, median, standard deviation, standard error of mean, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data. Where appropriate, p-values will be reported. All

statistical tests will be conducted using 2-sided tests with 5% Type I error rate unless otherwise stated.

PK parameters will be summarized by treatment group including number of patients, mean, standard deviation, coefficient of variation (CV), geometric mean, median, minimum, and maximum.

All eCRF data and data transfers from external vendors (e.g., laboratory, cognitive and neuropsychiatric testing) will be provided in the subject data listings. Patient data listings will be presented for all patients enrolled into the study.

Within this document, the terms 'patient' and 'subject' are both used to describe the individual who enrolls in this study. The terms 'MAD' and 'Part 1' may be used interchangeably. Similarly, the terms 'LTE' and 'Part 2' may be used interchangeably.

## 3.2 Analysis Periods, Analysis Groups, and Baseline definitions

The Analysis Periods, Analysis Groups (i.e. treatment groups), and Baseline definitions are given in the following sections. Please refer to Table B1, Table B2 and Table B3 in Appendix for more details.

### *3.2.1 Analysis Periods*

There are four periods which will be used for analysis and are defined as:

- MAD Period: Analyses include data from MAD, Part 1.
- LTE Period: Analyses include data from LTE, Part 2.
- MAD+LTE Period: Analyses include integrated data from both MAD, Part 1 and LTE, Part 2, regardless of a subject's randomization assignment or LTE enrollment status. For example, a subject receiving MAD placebo treatment who does not enroll in LTE will still contribute data from the MAD to this analysis.
- Active Treatment Period: Analyses include data from study periods in which a subject receives active ISIS 814907 treatment. (Note: Study periods refer to Part 1 and/or Part 2, including post-treatment follow-up but excluding any variable gaps in time between Part 1 and Part 2 for subjects in Cohorts A and B). Data collected during a placebo dosing period are not included (except relevant baseline data). Subjects who receive MAD active treatment will contribute data regardless of LTE enrollment status. Subjects who receive MAD placebo treatment will only contribute data if enrolled and dosed in the LTE.

In general, listings will be created for the MAD Period and the MAD+LTE Period.

Safety, pharmacodynamic and exploratory analyses will be conducted for the MAD Period and the LTE Period separately.

The MAD+LTE Period will be used to analyze select biomarkers, neuroimaging and key clinical assessments:

- MRI (exploratory)
- Tau-PET/FDG-PET
- CSF biomarkers including but not limited to total tau, phospho-tau and A-beta42
- MMSE
- RBANS
- CDR

The Active Treatment Period will be used to analyze select safety endpoints including:

- Laboratory assessments: Potential clinically significant laboratory abnormalities, hepatotoxicity, and shift analyses
- CSF Safety Panel
- Safety MRIs
- Incidence rates for treatment emergent adverse events (TEAEs) and serious TEAEs

### *3.2.2 Analysis Groups*

The analysis groups are described below according to the analysis periods in which they will be used.

#### *3.2.2.1 MAD Period*

- Pooled Placebo (excluding PK analyses): Cohorts A, B, C and D placebo-treated patients
- ISIS 814907 10mg Q4W: 10 mg ISIS 814907-treated patients
- ISIS 814907 30mg Q4W: 30 mg ISIS 814907-treated patients
- ISIS 814907 60mg Q4W: 60 mg ISIS 814907-treated patients
- ISIS 814907 115mg Q12W: 115 mg ISIS 814907-treated patients
- Total Active ISIS 814907 (excluding PK analyses): Cohorts A, B, C and D ISIS 814907-treated patients

#### *3.2.2.2 LTE Period, MAD+LTE Period, and Active Treatment Period*

The following analysis groups will be used for the LTE Period, MAD+LTE Period, and Active Treatment Period unless otherwise indicated. In case of very few subjects in any group, the analysis groups may be further pooled.

- Late Start A+B+C: MAD Cohorts A, B and C placebo-treated patients
- Late Start D: MAD Cohort D placebo-treated patients
- Early Start A: MAD Cohort A ISIS 814907-treated patients
- Early Start B: MAD Cohort B ISIS 814907-treated patients
- Early Start C: MAD Cohort C ISIS 814907-treated patients

- Early Start D: MAD Cohort D ISIS 814907-treated patients
- ISIS 814907 60 mg Q12W (LTE Period and Active Treatment Period):
  - LTE Period: All MAD Cohort A, B, and C roll-over subjects, regardless of randomization assignment. This group will be included for select analyses only in the LTE Period, e.g., AE and SAEs, safety analyses (except shift analyses for laboratory assessments), selected exploratory analyses only (including MRI volumetric, PET and clinical evaluations), PD and PK analyses.
  - Active Treatment Period: All MAD Cohort A, B, and C subjects, regardless of either randomization assignment or LTE enrollment status. This group will be included for select analyses only in the Active Treatment Period, e.g., serious TEAEs potentially related to Study Drug, overall summary of TEAEs, and safety MRIs.
- All Roll-over (LTE Period only, excluding PK analyses): All MAD Cohorts ISIS 814907-treated and placebo-treated roll-over patients.
- ISIS 814907 115 mg Q12W (LTE Period and Active Treatment Period): All MAD Cohort D roll-over subjects, regardless of randomization assignment (LTE Period). All MAD Cohort D subjects, regardless of either randomization assignment or LTE enrollment status (Active Treatment Period).
- Total Active (Active Treatment Period only, excluding PK analyses): All patients who receive at least 1 dose of ISIS 814907 in either the MAD or LTE periods.

In general, Early Start corresponds to a randomization assignment of active ISIS 804907 treatment in the MAD, whereas Late Start corresponds to a randomization assignment of Placebo in the MAD. The subjects and data which contribute to the analysis for a given population will be uniquely determined by both the Analysis period and Analysis group. For example, Early Start in the LTE Period includes data from subjects in the population randomized to active treatment during MAD who also enroll in the LTE; however Early Start in the MAD+LTE Period includes data from subjects in the population randomized to active treatment during MAD regardless of enrollment in the LTE.

### *3.2.3 Baseline definitions*

#### *3.2.3.1 MAD baseline*

MAD baseline will be used for the MAD and MAD+LTE analysis periods. It is defined as the last non-missing measure prior to the first dose of study drug in the MAD, except in the instances given below:

- For vital signs (blood pressure [BP] and heart rate [HR]), baseline will be defined as the average of the triplicate values collected on Day 1 pre-dose in the MAD. If only one or two assessments are available, the single assessment or average of the two assessments will be used.

- For ECG continuous parameters, baseline will be defined as the average of the triplicate values collected on Day -1 of the MAD. If only one or two assessments are available, the single assessment or average of the two assessments will be used. For ECG interpretation, baseline will be defined as the worst categorical results of the triplicate results collected on Day -1 of the MAD.
- For PD biomarkers, baseline will be defined as the average of the Screening and Day 1 pre-dose values in the MAD.
- For C-SSRS suicidal ideation score, baseline will be defined as the maximum score collected on Day -1 and Day 1 pre-dose in the MAD.

#### *3.2.3.2 Active treatment period baseline*

Active treatment period baseline will be used to analyze the LTE Period and the Active Treatment Period. Active treatment period baseline is the same as the MAD baseline for early start subjects, and for late start subjects is the last non-missing measure collected prior to the first dose of study drug in the LTE except in the instances below:

- For vital signs (blood pressure [BP] and heart rate [HR]), as the average of the triplicate values collected on Day 1 pre-dose in the LTE. If only one or two assessments are available, the single assessment or average of the two assessments will be used.
- For ECG continuous parameters, as the average of the triplicate values collected immediately prior to first dose in the LTE. For ECG interpretation, baseline will be defined as the worst categorical results of the triplicate results collected immediately prior to first dose in the LTE.
- For C-SSRS suicidal ideation score, as the maximum score collected on Day -1 and Day 1 pre-dose in the LTE.

### *3.2.4 Analytical visits*

All post-baseline data will be summarized using the visit labels provided in the data. Multiple results with the same visit label will be averaged for the continuous variables, and the worst result will be used for the categorical variables. Results with visit labels as “Unscheduled” will be presented in data listing, but not be included in the by-visit summary tables and figures, except for determining baseline.

## 3.3 Sample Size Considerations

While there is no statistical rationale for the sample size, it has been selected based on prior experience with generation 2.0 ASOs (Tabrizi et. al, 2019) given by IT bolus injection to ensure that the safety, tolerability, PKs, and exploratory pharmacodynamics will be adequately assessed while minimizing unnecessary patient exposure.

## 3.4 Statistical Methods

### *3.4.1 Patient Population Analyzed*

The following analysis populations are defined for this study:

- ITT Population: All patients who are randomized and receive at least 1 dose of Study Drug (ISIS 814907 or placebo).
- Safety Population: All patients who are randomized and receive at least 1 dose of Study Drug (ISIS 814907 or placebo).
- PK Population: All patients who are randomized, receive at least 1 dose of ISIS 814907 and have sufficient sampling (at least one evaluable post-baseline PK sample) to permit PK evaluation.

The ITT population will be used for all demographic, baseline characteristics, PD and exploratory analyses. The safety population will be used for all safety analyses. PK population will be used for PK analyses.

A Per Protocol population may be considered for select analyses if necessary.

As previously indicated, the population will be used in conjunction with the analysis periods and analysis groups to uniquely indicate the subjects and data contributing to the analyses. For example, an analysis of the safety population in the Active Treatment Period for late start subjects will include data from the LTE period for subjects who were randomized and received at least one dose of study drug.

### *3.4.2 Handling of Missing Data*

Unless otherwise specified, missing values will not be imputed.

### *3.4.3 Planned Interim Analysis*

#### *3.4.3.1 End of MAD, Part 1*

An interim analysis of the MAD Period to investigate safety, PK, PD and exploratory endpoints will be conducted at the end of MAD, Part 1 when the last patient completes the last visit, and the results will be summarized by treatment group. Unblinded data will be evaluated at this analysis. All patients/all data through the end of MAD, Part 1 will be used for the analysis with the exception of CSF biomarkers data (through Day 1 pre-dose in LTE, Part 2). The individuals involved in the unblinded interim analysis will be identified and documented at the time of unblinded interim analysis according to Ionis standard operation procedure (SOP). The investigators, patients and study center personnel, including the site pharmacist, will be blinded to treatment assignment from the MAD for the duration of the study (i.e., until the end of LTE).

The MAD Period will be analyzed during this IA. The analysis of the LTE, MAD+LTE, and Active Treatment Periods will be performed following the final study lock after completion of the LTE period.

#### *3.4.3.2 Safety monitoring review*

A formal safety monitoring group (FSMG) will be assembled to review unblinded safety, tolerability, PK, and target engagement/PD (as needed) data collected during this study. The FSMG group is comprised of at least three medical doctors, all experienced in the conduct of clinical studies in patients with neurodegenerative diseases and otherwise independent from the conduct of the study. Unblinded statisticians or designees who will not be involved in the study conduct will generate and distribute the data to the FSMG prior to each meeting. Based on its ongoing assessment of the study data, the FSMG will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the assessments, frequency of review, meeting schedules and controlled access to unblinded data will be outlined in the FSMG charter.

### *3.4.4 Demographic and Baseline Characteristics*

Demographic and Baseline characteristics will be summarized using descriptive statistics by analysis group based on the ITT population for the MAD, LTE and Active Treatment Periods separately.

Demographics include age, gender, ethnicity, race, education level in ISCED, weight, height, BMI. Height was measured at MAD Screening only, at other visits other than Screening, BMI ($kg/m^2$) could be computed using the formula:

$$\text{BMI} = (\text{weight in kilograms}) / [\text{height in cm} / 100]^2.$$

Baseline characteristics include individual patient CSF volume (spinal CSF volume, cranial CSF volume, and total CSF volume) and brain volumes (whole brain, ventricular, left and right hippocampal volumes), ARWMC total score; C-SSRS suicidal ideation score and clinical assessment scales (RBANS, MMSE, FAQ, NPI-Q, MHIS, CDR global and memory score, CDR Sum of Boxes, GDS-SF); CSF AD biomarkers (total tau, phospho-tau, A-beta42), CSF NfL & total NfH; prior and concomitant anti-dementia medication (cholinesterase inhibitors and memantine), estrogen replacement therapy, low dose antipsychotic medication, aspirin, fish-oil; and genetic profile (APOE, CD33, BCHE, H1 MAPT haplotype).

### *3.4.5 Disposition of Subjects*

Patient enrollment and disposition for the MAD and LTE Periods will be summarized for each treatment group, and for all patients. By-subject disposition listings for all randomized subjects and for screen failures will also be provided for the MAD and MAD+LTE Periods.

- The summaries for the MAD Period will include: the total number of screened patients, the number of patients screen failures, the number and percentage of randomized patients, the number and percentage of patients in each analysis population the number and percentage of patients who completed the study treatment, the number and percentage of patients who terminated treatment and reason, the number and percentage of patients who completed post-treatment follow-up, and the number and percentage of patients who terminated post-treatment follow-up and reason.
- The summaries for the LTE Period will include: the number of patients that transitioned into the LTE (i.e., total number, and breakdown of number of patients by MAD dose cohort), the number of patients that did not transition into the LTE and reason, the number of patients who were registration screen failures and reason for Cohorts A and B, the number and percentage of patients in each analysis population, the number and percentage of patients completed the study treatment, the number and percentage of patients who terminated treatment and reason, the number and percentage of patients completed post-treatment follow-up, and the number and percentage of patients terminated post-treatment follow-up and reason.

Study terminations and LTE registration screen failures that are due to COVID-19 related impact will be included in the above-mentioned summary tables and subject listings.

### *3.4.6 Protocol Deviations*

Protocol deviations will be classified to major or minor based on the study protocol deviation process plan. Protocol deviations will be provided in the data listings. Additional table may be provided to summarize the protocol deviations related to COVID-19.

A listing of all patients affected by the COVID-19 related study disruption by subject number identifier and by investigational site, and a description of how the individual's participation was altered will be provided.

Listing of medical history will be provided.

Subject listings will be performed for the MAD and MAD+LTE Periods.

## 3.5 Safety Analyses

The safety analyses for the MAD Period, the LTE Period, and the Active Treatment Period will be conducted on the Safety Population.

### *3.5.1 Exposure*

Treatment duration, total amount of study drug (MAD: ISIS 814907 or placebo; LTE and Active Treatment periods: ISIS 814907) received (mg), and number of doses administered will be summarized by analysis group for the MAD, LTE, and Active Treatment Periods.

The treatment duration (days) for each subject is defined as:

- MAD Period, LTE Period separately: last dose date within the Period – first dose date within the Period + 1
- Active Treatment Period, early starters: [(last dose date in MAD – first dose date in MAD + 1) + (last dose date in LTE – first dose date in LTE + 1)]. For subjects not enrolled in LTE then it is the same as the MAD Period exposure
- Active Treatment Period, late starters: (last dose date in LTE – first dose date in LTE + 1).

### *3.5.2 Time on Study Analysis*

The time on study analysis described below will be included in the final analysis only.

Time on study (years) will be summarized by analysis group for the MAD, LTE, MAD+LTE and Active Treatment Periods using descriptive statistics. Total time on study (patient-years) in each analysis group will be included in the summaries.

Additionally for the MAD+LTE Period, time from last dose date in MAD to first dose date in LTE (years), and time from last study visit date in MAD to first dose in LTE (days and years, separately) will be summarized by analysis group using descriptive statistics.

Time on study (days) for each subject is defined as:

- MAD Period, LTE Period separately: last study visit date within the Period – first dose date within the Period + 1
- Active Treatment Period, early starters: (last study visit date in MAD - first dose date in MAD + 1) + (last study visit date in LTE – first dose date in LTE + 1). For subjects not enrolled in LTE then it is the same as the MAD Period time on study.
- Active Treatment Period, late starters: last study visit date in LTE - first dose date in LTE + 1.
- MAD+LTE Period: (last study visit date in MAD – first dose date in MAD + 1) + (last study visit date in LTE – first dose date in LTE + 1). For subjects not enrolled in LTE then it is the same as the MAD Period time on study.

Time on study (years) for each subject is calculated as the time on study (days) divided by 365.25. Total time on study (patient-years) is calculated as the sum of time on study (years) across subjects within the analysis group and period.

For the MAD+LTE Period: Time from last dose date in MAD to first dose date in LTE (years) is defined as: (first dose date in LTE – last dose date in MAD + 1)/365.25. Time from last study visit date in MAD to first dose in LTE (days) is defined as: first dose in LTE – last study visit

date in MAD + 1; Time from last study visit date in MAD to first dose in LTE (years) is: (first dose in LTE – last study visit date in MAD + 1)/365.25.

### *3.5.3 Adverse Events*

#### *3.5.3.1 MAD Period and LTE Period*

The incidence (proportion) of treatment-emergent adverse events (TEAEs) will be summarized for the MAD and LTE Periods separately, and incidence (rates) of TEAEs will be summarized for the Active Treatment period where indicated by *. The Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 will be used. Summaries will be presented by preferred term (PT) and system organ class (SOC), unless otherwise indicated, for:

- Any TEAE* (summarized by PT only and by both SOC and PT)
- TEAEs potentially related to Study Drug. Related is defined as “Related”, “Possible”, or missing relationship to study drug, as determined by the investigator
- TEAEs potentially related to Lumbar Puncture (LP) procedure. Related is defined as “Related”, “Possible”, or missing relationship to LP procedure
- Any TEAE by severity*. At each level of subject summarization, a subject is classified according to the highest severity if the subject reported one or more events. TEAEs with missing severity will be categorized as “Missing” for this summary
- TEAEs potentially related to Study Drug by severity
- TEAEs potentially related to LP procedure by severity
- Serious TEAEs* (by PT only and by both SOC and PT)
- Serious TEAEs potentially related to Study Drug*
- Serious TEAEs potentially related to LP procedure*
- TEAEs leading to permanent study drug discontinuation* (by PT only and by both SOC and PT)

The number and proportion of LPs leading to TEAEs will be summarized for the MAD and LTE Periods separately. The severity of AEs and SAEs will be graded based on criteria from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, June 2010. SAEs and non-serious AEs that lead to permanent study drug discontinuation will be listed separately. Non-treatment emergent adverse event will be flagged in the data listing.

An adverse event will be regarded as treatment emergent if it is present prior to receiving the first dose of study drug (MAD: ISIS 814907 or placebo; LTE and Active Treatment Periods: ISIS 814907) and subsequently worsened, or is not present prior to receiving the first dose of

study drug (MAD: ISIS 814907 or placebo; LTE and Active Treatment Periods: ISIS 814907) but subsequently appeared.

If there is no "Formlink" link, and the AE (start date/time) occurs after the subject's first dosing date/time, then the AE is treatment-emergent. Otherwise, if the AE (start date/time) occurs prior to the subject's first dosing date/time, then the AE is not treatment-emergent.

If there is a "Formlink" link between two AE records, then we compare them pairwise, and consider two cases, where we compare the AE severity (mild/moderate/severe) between the two records in the pair. We chronologically order the 2 records (by AE start date) and refer to the "first" and "second" AEs.

Case 1: The first AE record in the pair occurs before first dosing, and the second AE record occurs after first dosing.

If the AE severity or seriousness of the second record is worse than that of the first record, then only the second AE is deemed as TEAE. Otherwise, neither record is considered as TEAE.

Case 2: Both AE records in the pair occur after first dosing.

The worst AE will be deemed as a TEAE.

All TEAEs identified based on the rules above will be summarized in the event number analysis.

The most conservative approach will be used to determine if the event occurs after the treatment. For example, if the onset date or resolution date of an AE is prior to the first study treatment date, it will be considered to have occurred prior to the study period. If the onset or resolution date of an AE is a partial date with only month or year available or completely missing, then the event is assumed to be within the study period unless the year is prior to the year of the first study treatment date, or if in the same year, the month is prior to the month of the first study treatment date.

#### *3.5.3.2 Incident rates calculation for Active Treatment Period*

Incidence rates of AEs which adjust for patient-years on study will be summarized for the Active Treatment Period as indicated previously. The total time on study (patient-years) will be calculated as described in Section 3.5.2. Incidence per 100 patient-years on study will be presented, defined as: [Number of subjects reporting at least one AE during the period / Total time on study (patient-years)] × 100.

### *3.5.4 Prior and Concomitant Medications*

Prior and concomitant medications will be coded using WHO Drug dictionary (WHO-DD, Version SEP 2017) and summarized by ATC class, generic name/preferred medical name and by treatment group for the MAD Period and LTE Period separately.

A concomitant medication is defined as medications that were taken on or after the first day of study drug administration within the analysis period. This includes medications that were started prior to the initiation of study drug if their use continued on or after the date of the first dosing. In order to define concomitant medications with missing start or stop dates, the following additional criteria will be used:

- if both the start and stop dates of a particular medication were missing, that medication is considered concomitant;
- if the start date of a medication was missing and the stop date of that medication fell on or after the date of dosing, that medication is considered concomitant;
- if the start date of a medication was prior to the date of first dosing and the stop date of that medication was missing, that medication is considered concomitant; or
- if the start/stop date of a medication is partial then where it is not possible to rule out that it was not taken concomitantly it will be considered concomitant.

Non concomitant medications will be flagged in the data listing.

### *3.5.5 Columbia Suicide Severity Rating Scale (C-SSRS)*

Per study design, the C-SSRS assessments will be scheduled in Part 1 and Part 2.

The C-SSRS collects binary Yes/No responses to 11 categories: five subtypes of suicidal ideation and five subtypes of suicidal behavior, and self-injurious behavior without suicidal intent. Specifically, the following outcomes are C-SSRS categories and have binary (Yes/No) responses. (The categories have been re-ordered from the actual scale to facilitate the definitions of the composite endpoints and to enable clarity in the presentation of the results (Nilsson et. al, 2013).

Suicidal Ideation:

Category 1 – Wish to Be Dead

Category 2 – Non-specific Active Suicidal Thoughts

Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act

Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan

Category 5 – Active Suicidal Ideation with Specific Plan and Intent

Suicidal Behavior:

Category 6 – Preparatory Acts or Behavior

Category 7 – Aborted Attempt

Category 8 – Interrupted Attempt

Category 9 – Actual Attempt (non-fatal)

Category 10 – Completed Suicide

Other:

Category 11 – Non-suicidal Self-Injurious Behavior

A numerical score, the Suicidal Ideation Score, will be defined as the highest suicide ideation category (1–5) at which the patient responded "Yes" for the given visit. If the patient did not respond "Yes" to any of these categories, the score will be set to zero. The baseline suicidal ideation score will be summarized as baseline characteristics.

The C-SSRS will be analyzed for the MAD Period and LTE Period separately. For each of the categories above, the number and percent of patients with a "Yes" response at any time post-baseline (regardless of baseline response) will be summarized by treatment group. C-SSRS results will be listed for the MAD and MAD+LTE Periods. All data from patients with a "Yes" response at any time post baseline will be listed separately.

### *3.5.6 Laboratory Measurements*

The following is the list of lab analytes that will be measured throughout the study:

- Chemistry: Sodium, Potassium, Chloride, Total protein, Albumin, Calcium, Magnesium, Phosphorus, Bicarbonate, Glucose, BUN, Creatinine, Total serum Bilirubin, Uric acid, Alkaline phosphatase, AST (SGOT), ALT (SGPT), GGT and CPK.
- Hematology: Red blood cells, Hemoglobin, Hematocrit, Platelets, MCV, MCH, MCHC, White blood cells (WBC), and WBC Differential (percentage and absolute count) (Neutrophils, Eosinophils, Basophils, Lymphocytes and Monocytes)
- Coagulation: aPTT, PT, INR
- Thyroid Panel: TSH, Free T4, and Free T3
- PK: Plasma and CSF ISIS 814907 levels
- CSF Safety Panel (Minimum Requirements): Red blood cells, WBC, Glucose, Protein and Albumin
- Urinalysis: Specific gravity, pH, Protein, Glucose, Ketones, Urobilinogen, Leukocyte esterase, Nitrite, Bilirubin, Blood, Red blood cells, WBC, Epithelial cells, Bacteria, Casts, Crystals, Color and Appearance and P/C ratio
- Additional Safety Tests (plasma): Immunogenicity. (Note: samples have been collected but will not be analyzed.)

In addition:

- Plasma/serum tests measured at screening in Part 1 of the study only: Hepatitis B surface antigen, Hepatitis C antibody, HIV antibody, FSH (women only), Drug/Alcohol Screen, serum folate, serum B12, serum homocysteine, serum uric acid, Treponemal antibody
- CSF tests measured at screening in Part 1 of the study only: CSF homocysteine, folate, B12

Genetic testing is performed at Day -1 in Part 1 of the study will include: *APOE*, *BCHE*, *IL1RAP*, *CD33, H1 MAPT haplotype*, *APP*, *PSEN1*, *PSEN2*.

Missing WBC differential absolute counts and percentages will be derived as below:

If WBC differential absolute counts are missing, and percentages are available, then absolute counts will be calculated by multiplying the percentage by total WBC count. Conversely, if absolute count is available, and percentage is missing, then percentage will be calculated by dividing absolute count by the total WBC count. If neutrophils counts and percentages are missing, and segmented neutrophil and band neutrophil results are available, then neutrophils will be calculated by adding segmented neutrophils and band neutrophils.

Laboratory tests to ensure patient safety include clinical chemistry panel, hematology panel, coagulation, urinalysis and safety CSF labs (Red blood cells, WBC, Glucose, and Protein), will be summarized by treatment group and each post-baseline visit for the MAD and LTE Periods separately. These safety variables will also be presented as change and percent change from baseline over time after Study Drug administration, as appropriate.

In addition, shift tables will be done for the MAD, LTE, and Active Treatment periods. The shifts (relative to the normal range) from baseline to the minimum and maximum post-baseline values, or shifts to abnormal, as appropriate, for each specific laboratory parameter in the following categories: CSF safety panel, coagulation, hematology, chemistry, and urinalysis (excluding microscopic examination) will be presented. If a subject is missing a baseline value but had a post-baseline value, then the baseline assessment is labeled as “unknown”. Likewise, if a subject had a baseline value but had no post-baseline values, then the minimum and maximum are labeled as “unknown”. For each parameter, the incidence of shift to low will be summarized using the minimum post-baseline values; the incidence of shift to high will be summarized using the maximum post-baseline values.

Only central laboratory data will be used for the summary tables and figures. Local laboratory data will be provided in the listings only, except for local results for CSF safety tests which will be listed and summarized in tables.

Individual data listings of all laboratory results for MAD Period and MAD+LTE Period will be presented for each subject. All values outside the clinical reference ranges will be flagged in the data listings. The abnormal value is defined as the value below the lower limit or above the upper limit of the clinical reference range. Abnormal laboratory results for the MAD and MAD+LTE Periods will also be displayed in separate listings.

#### *3.5.6.1 Potential clinically significant laboratory abnormalities*

For hematology, blood chemistry and urinalysis, the number of subjects with potentially clinically significant (PCS) laboratory abnormalities post-baseline will be summarized for the parameters provided in Table 1 for the MAD, LTE, and Active Treatment analysis periods.

Subjects need to have at least one post-baseline evaluation and a baseline value not potentially clinically significant (including missing) in order to be included in the analysis.

For the LTE and the Active Treatment period analyses, the active treatment period baseline will be used. For early start subjects, PCS abnormalities that occurred in either MAD or LTE will be included in the active treatment period analysis, whereas PCS abnormalities that occurred in the LTE will be included in the LTE analysis. For late start subjects, PCS abnormalities that occurred in the LTE period will be included.

**Table 1: Clinical laboratory outlier criteria**

| Parameter name | PCS Low | PCS High |
|---|---|---|
| **HEMATOLOGY** | | |
| White blood cells (Leucocytes) | <3.0 x $10^9$/L | >16 x $10^9$/L |
| Absolute Lymphocyte Count | <0.8 x $10^9$/L | >12 x $10^9$/L |
| Absolute Neutrophil Count | <1.5 x $10^9$/L | >13.5 x $10^9$/L |
| Absolute Monocyte Count | N/A | >2.5 x $10^9$/L |
| Absolute Eosinophil Count | N/A | >1.6 x $10^9$/L |
| Absolute Basophil Count | N/A | >1.6 x $10^9$/L |
| Red blood cell (Erythrocyte) Count | ≤3.5 x $10^{12}$/L | ≥6.4 x $10^{12}$/L |
| Hemoglobin - Females | ≤95 g/L | ≥175 g/L |
| Hemoglobin - Males | ≤115 g/L | ≥190 g/L |
| Hematocrit - Females | ≤0.32 L/L | ≥0.54 L/L |
| Hematocrit - Males | ≤0.37 L/L | ≥0.60 L/L |
| Platelets | ≤75 x $10^9$/L | ≥700 x $10^9$/L |
| **BLOOD CHEMISTRY** | | |
| Alanine aminotransferase (ALT) | N/A | >3 x ULN |
| Aspartate aminotransferase (AST) | N/A | >3 x ULN |
| Alkaline phosphatase (ALP) | N/A | >3 x ULN |
| Total bilirubin | N/A | >1.5 x ULN |
| Blood urea nitrogen (BUN) | N/A | ≥10.7 mmol/L |
| Creatinine | N/A | ≥176.8 umol/L |
| Sodium | ≤126 mmol/L | ≥156 mmol/L |
| Potassium | ≤3 mmol/L | ≥6 mmol/L |
| Chloride | ≤90 mmol/L | ≥118 mmol/L |
| Glucose | ≤2.2 mmol/L | ≥9.7 mmol/L |
| Calcium | ≤2 mmol/L | ≥3 mmol/L |
| Phosphorus | ≤0.6 mmol/L | ≥1.7 mmol/L |
| Albumin | ≤25 g/L | ≥625 g/L |
| Total protein | ≤45 g/L | ≥100 g/L |
| Creatine Kinase | N/A | ≥1000 IU/L |
| **URINALYSIS** | | |
| Glucose | N/A | ≥ 1000 mg/dL; 4+ |
| Protein | N/A | ≥ 100 mg/dL; 2+ or higher |

Note: ULN = upper limit of normal
The clinical laboratory outlier criteria are shown in SI units in this table.

#### *3.5.6.2 Potential serious hepatotoxicity*

Potential serious hepatotoxicity will be analyzed for the MAD, LTE, and Active Treatment Period. Potential serious hepatotoxicity is defined as a confirmed ALT or AST > 3x ULN and confirmed total bilirubin > 2x ULN at any time post-baseline in the analysis period, not necessarily concurrent. A scatterplot of the maximum post-baseline ALT or AST value relative to ULN and maximum post-baseline total bilirubin value relative to ULN (not necessarily concurrent) for each subject will be provided. A spaghetti plot of ALT, AST, ALP and total bilirubin values over time for subjects with potential serious hepatotoxicity will be provided. In addition, subjects with ALT > 1x ULN, >3x ULN, >5x ULN, >10x ULN or >20x ULN, subjects with AST > 1x ULN, >3x ULN, >5x ULN, >10x ULN or >20x ULN, subjects with total bilirubin >1x ULN or >2x ULN, subjects with ALP >1x ULN or >1.5x ULN, and subjects with AST or ALT > 3x ULN post-baseline accompanied by concurrently elevated total bilirubin >1.5x ULN or > 2x ULN will be presented. Concurrent is defined as on the same day. A listing of subjects with potential serious hepatotoxicity will be provided.

A confirmed value is based on a consecutive lab value performed on a different day to, but within 7 days of, the initial value. If the consecutive value is in the same or worse ULN criteria described above, then the initial value is confirmed. If there is no retest within 7 days, then the initial value is presumed confirmed. If there are multiple results on the same day (no matter from the same lab vendor or different lab vendors), then the worst value will be utilized in the analysis.

### *3.5.7 Vital Signs Measurements*

Vital signs will include heart rate, respiratory rate, body temperature, body weight, seated and standing systolic and diastolic blood pressure and pulse, and orthostatic changes.

Orthostatic changes include 3 variables: change from seated systolic blood pressures to average of all available standing systolic blood pressures, change from seated diastolic blood pressure to average of all available standing diastolic blood pressure, and change from seated heart rate to average of all available standing heart rate.

Summary tables will be created for the MAD and LTE Periods separately to present the descriptive statistics for vital sign values as well as the change and percent change from baseline at each post-baseline visits.

### *3.5.8 12-Lead Electrocardiograms (ECG)*

Safety 12 lead ECG will be performed in triplicate at the visits indicated in the protocol Schedule of Procedures. ECG data will be collected through a central reader.

The ECG data will include ventricular rate (VR), PR interval, QRS duration, QT, QTcF (QT corrected using the Fridericia's formula), and QTcB (QT corrected using the Bazett's formula).

QTcF and QTcB will be calculated based on the subject's reportable ECG data at each time point using the formula described below:

$QTcF = QT / (RR)^{1/3}$, where $RR = 60 / VR$

$QTcB = QT / (RR)^{1/2}$, where $RR = 60 / VR$

At Screening visit, three replicates of ECG parameters will be recorded, and the mean from all replicates will be used as the patient's reportable value at Screening visit. Only calculated QTcB and QTcF will be summarized and included in the data listing. The QTC value recorded on the CRF will not be summarized and will be excluded from the data listing.

For the continuous variables, the average of measurements at a given visit will be used for analysis. For overall interpretation, the worst categorical results of triplicate results and the associated findings will be used for analysis. Summary tables will be created for the MAD and LTE Period respectively to present the descriptive statistics of the actual values, the change and percent change from baseline at each study visit for continuous variables above; and counts and percentages at each study visit for categorical responses to overall interpretation.

Criteria for potentially clinically significant used to define post-Baseline QTcB and QTcF categorization are as follows: ≤ 450 msec, >450 msec to ≤ 480 msec, >480 msec to ≤ 500 msec and >500 msec for measured values as well as >30 msec and >60 msec for changes from Baseline. The number and percentage of subjects reporting a category will be presented by treatment group, separately for QTcB and QTcF. Subjects will be counted only once if they had more than one such event during the analysis period, so only a subject's worst post-Baseline value will be considered.

All the ECG data collected in triplicate, except the CRF QTC value, will be listed.

### *3.5.9 Physical and Neurological Examinations*

The physical & neurological examinations for the MAD and MAD+LTE Periods will be provided in patient listings.

### *3.5.10 Safety Neuroimaging Assessments*

MRI safety sequences (T2 FLAIR, GRE T2 star, T2 Fast Spin Echo [FSE]/Turbo Spin Echo [TSE], Diffusion Tensor Imaging [DTI]) will be performed to characterize the patients' pre-treatment and post-treatment state, at Screening and Day 169 (post-treatment period) in Part 1, and at the Registration Visit (patients who are not seamlessly transitioning only), at Day 252 (or Day 336 if not performed at Day 252) and Day 449 (post-treatment period) in Part 2.

Safety MRI will be summarized for the MAD Period, LTE Period and Active Treatment Period by analysis group. During the MAD Period, the number of subjects with an increased number of microhemorrhages at Day 169 in comparison to baseline, and the number of subjects with an increased white matter disease total score at Day 169 in comparison to baseline will be

presented. Treatment-emergent (TE) brain MRI abnormalities are those occurring at Day 169 which are new (were not present at baseline) or which are worsening (were present at baseline and have a status of 'still present and increased in size' at Day 169). The number of subjects with any TE brain MRI abnormality will be summarized, as well as those with any new TE brain abnormality, and with any worsening TE brain MRI abnormality. The number of subjects with a specific type (e.g., macrohemorrhages) of new abnormality will be presented; similarly, the number with a specific type of worsening abnormality will be presented. During the LTE Period, similar analysis will be performed by analysis group at Registration Visit Part 2, Day 252 Part 2 (or Day 336 if not performed at Day 252 Part 2), and Day 449 Part 2. During the Active Treatment Period, similar summaries will be conducted by analysis group at Day 169 Part 1, Registration Visit Part 2, Day 252 Part 2 (or Day 336 if not performed at Day 252 Part 2), and Day 449 Part 2.

Safety MRI for the MAD Period and the MAD+LTE Period will be presented in data listings.

## 3.6 Pharmacokinetic Analysis

CSF and Plasma samples will be collected at protocol designated times for ISIS 814907 pharmacokinetic assessments from the dose cohorts. Only concentration data from patients randomized to receive study drug (ISIS 814907) will be included in this analysis. The PK analyses will be performed for the MAD Period and LTE Period separately according to the analysis groups given in Section 3.2.2.

### *3.6.1 CSF Concentration Data and Pharmacokinetics*

A CSF sample will be collected pre-dose on each injection day in the MAD and LTE and during post-treatment evaluation periods in the MAD and LTE for PK analyses. CSF concentrations of ISIS 814907, along with the scheduled (nominal) and actual samples times (i.e., time from IT dosing) will be listed (when applicable) for each patient, analysis group, nominal dose, and day. Differences between scheduled and actual sampling days will also be listed for all patients, as well as percent differences between actual administered dose and nominal dose.

CSF concentrations below the lower limit of quantification (LLOQ) will be indicated by "BLQ". For the purpose of calculating typical descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) for CSF concentrations, all BLQ values will be set to LLOQ/2 after the first active dose and will be set to 0 prior to the first active dose. Mean CSF concentrations that are BLQ will be presented as BLQ, and the SD and %CV will be reported as not applicable. Summary statistics of the ISIS 814907 CSF concentrations will be tabulated for the MAD and LTE Periods separately by analysis group, nominal dose and day. At the discretion of the pharmacokineticist and/or biostatistician, samples may be excluded from descriptive statistics if there are large deviations between scheduled and actual sampling days, or large deviations between actual dose and nominal dose.

The ISIS 814907 half-life in CSF will be calculated, if possible, for the MAD Period and summarized by analysis group, nominal dose, and nominal day.

ISIS 814907 CSF concentration versus time (actual) profiles from Day 1 to last collection, for each patient, as well as the mean (±SE) CSF concentration versus time (scheduled) profiles for each treatment cohort, will be presented graphically on linear scale for the MAD and LTE Periods separately. Samples may be excluded from the mean plots if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

### *3.6.2 Plasma Concentration Data*

Plasma concentrations of ISIS 814907, along with the scheduled (nominal) and actual samples times (i.e., time from IT dosing) will be listed (when applicable) for each patient, analysis group, nominal dose, and day. Percent differences between scheduled and actual sampling times will also be listed for all patients as well as percent differences between actual administered dose and nominal dose.

Plasma concentrations below the lower limit of quantification (LLOQ) will be indicated by "BLQ". For the purpose of calculating typical descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) for plasma concentrations, all BLQ values will be set to LLOQ/2 with the exception of concentration prior to the first dose which will be set to '0'. Mean plasma concentrations that are BLQ will be presented as BLQ, and the SD and %CV will be reported as not applicable. Summary statistics of the ISIS 814907 plasma concentrations will be tabulated for the MAD and LTE periods separately by analysis group, nominal dose, day, and scheduled time point. At the discretion of the pharmacokinetic scientist and/or biostatistician, samples may be excluded from descriptive statistics if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

ISIS 814907 plasma concentration versus time (actual) profiles from Day 1 (MAD and LTE Periods), Day 29 (MAD period), Day 85 up to Day 141 (MAD period), and Day 337 up to Day 421 (LTE period), for each patient, as well as the mean (±SE) plasma concentration versus time (scheduled) profiles by analysis group will be presented graphically on linear and semilogarithmic scales. Additionally, ISIS 814907 plasma concentration versus time (actual) profiles from 0 to 24 hours on Days 1 and 85 (MAD period) and Days 1 and 337 (LTE period) for all patients, as well as the mean (±SE) plasma concentration versus time (scheduled) profiles (0 to 24 hours on Days 1 and 85 [MAD period]; 0 to 24 hours on Days 1 and 337 [LTE period]) for each analysis group will be presented graphically on linear and semilogarithmic scales. Samples may be excluded from the mean plots if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

### *3.6.3 Plasma Pharmacokinetics*

Non-compartmental pharmacokinetic analysis of ISIS 814907 will be carried out on each individual patient data set using Phoenix WinNonlin version 6.3 or higher (Pharsight Corporation, Mountain View, CA). Plasma pharmacokinetic parameters in each patient (when applicable) will be determined. For calculation of PK parameters, all BLQ values will be set to zero. The following plasma PK parameters will be calculated (when applicable) and based on actual sampling times:

**Table 2: Plasma PK parameters in Part 1-MAD and Part 2-LTE**

| **Part 1 – MAD** | | | |
|---|---|---|---|
| **Parameter** | **Definition/Method** | **Day 1** | **D85** |
| $C_{max}$ | Maximum observed concentration | X | X |
| $T_{max}$ | Observed time at which $C_{max}$ occurs | X | X |
| $T_{last}$ | Time of last measurable (positive) concentration | X | X |
| $AUC_{0\text{-}24hr}$ | Partial AUC: Area under the concentration-time curve from time zero to 24 hours post dose, calculated using linear-up log-down method. | X | X |
| $AUC_{0\text{-}28days}$ | Partial AUC: Area under the concentration-time curve from time zero to 28 days), calculated using linear-up log-down method (aka, $AUC_{\tau}$) | | X |
| $t_{1/2\lambda z}$ | Terminal elimination half-life determined from the equation: ln 2/$\lambda_z$, where $\lambda_z$ is the first-order rate constant associated with the terminal (log-linear) elimination phase. This is estimated via linear regression of time vs. log concentration. A minimum of three data points in the elimination phase will be used to define $\lambda_z$ and the correlation of determination values ($r^2$) had to be at or greater than 0.8 for the estimate to be accepted. | | X |
| $CL_{ss}/F$ | Steady-state clearance divided by F (fraction of the dose absorbed) determined by $Dose/AUC_{0\text{-}28days}$ | | X |
| $CL_{0\text{-}24hr}/F$ | Clearance after first dose divided by F (fraction of the dose absorbed) determined by $Dose/AUC_{0\text{-}24hr}$ | X | |
| $V_z/F$ | Volume of distribution (based on the terminal phase) divided by F (fraction of the dose absorbed) | | X |
| **Part 2 – LTE** | | | |
| **Parameter** | **Definition/Method** | **Day 1** | **D337** |
| $C_{max}$ | Maximum observed concentration | X | X |
| $T_{max}$ | Observed time at which $C_{max}$ occurs | X | X |
| $T_{last}$ | Time of last measurable (positive) concentration | X | X |
| $AUC_{0\text{-}24hr}$ | Partial AUC: Area under the concentration-time curve from time zero to 24 hours post dose, calculated using linear-up log-down method. | X | X |
| $AUC_{0\text{-}28days}$ | Partial AUC: Area under the concentration-time curve from time zero to 28 days), calculated using linear-up log-down method (aka, $AUC_{\tau}$) | | X |
| $t_{1/2\lambda z}$ | Terminal elimination half-life determined from the equation: ln 2/$\lambda_z$, where $\lambda_z$ is the first-order rate constant associated with the terminal (log-linear) elimination phase. This is estimated via linear regression of time vs. log concentration. A minimum of three data points in the elimination phase will be used to define $\lambda_z$ and the correlation of determination values ($r^2$) had to be at or greater than 0.8 for the estimate to be accepted. | | X |
| $CL_{ss}/F$ | Steady-state clearance divided by F (fraction of the dose absorbed) determined by $Dose/AUC_{0\text{-}28days}$ | | X |
| $CL_{0\text{-}24hr}/F$ | Clearance after first dose divided by F (fraction of the dose absorbed) determined by $Dose/AUC_{0\text{-}24hr}$ | X | |
| $V_z/F$ | Volume of distribution (based on the terminal phase) divided by F (fraction of the dose absorbed) | | X |

Plasma pharmacokinetic parameters (if applicable) will be summarized using descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) treatment cohort, nominal dose, and day.

Other PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

## 3.7 Pharmacodynamic and Exploratory Analysis

The pharmacodynamic and exploratory analyses, including evaluation of target engagement (total tau and phosphor-tau), will be conducted on the ITT population for the MAD, LTE, and MAD+LTE (where indicated) Periods.

Exploratory analyses of covariates of interest may be performed as post hoc analysis to evaluate their association with changes from baseline in neuroimaging parameters, cognitive assessments, or PK/PD and safety parameters. Covariates of interest may include, but are not limited to, demographics, medical history, concomitant medications, baseline characteristics (i.e., biomarkers, cognitive assessments, genotype and neuroimaging parameters).

### *3.7.1 Biochemical Analysis*

Total tau in CSF is the key exploratory endpoint for the study. Other potential CSF biomarkers included in the analysis are target engagement (phospho-tau), A-beta42, A-beta40, total tau to A-beta42 ratio, A-beta42 to A-beta40 ratio, NfL, total NfH, neurogranin, YKL-40. If total tau to A-beta42 ratio is missing, but total tau and A-beta42 are available, then total tau to A-beta42 ratio will be derived as total tau divided by A-beta42. A-beta42 to A-beta40 ratio will be derived as A-beta42 divided by A-beta40.

In the MAD Period, the actual values, change, and percent change from baseline for CSF biomarkers at each visit will be summarized using descriptive statistics. CSF biomarkers at Day 1 (pre-dose) visit in the LTE will also be added in the MAD Period analysis. The absolute change and percent change from baseline for CSF biomarkers at each post-baseline visit will be compared between ISIS814907-treated groups and the pooled placebo group. The absolute changes from baseline at each post-baseline visit will be compared between each ISIS 814907 treated analysis group and pooled placebo using the ANCOVA with baseline value as covariate or Wilcoxon Rank Sum test, as appropriate. Since the percent change from baseline for biochemical data is not always normally distributed, an analysis of covariance (ANCOVA) model will be fit to the log-transformed data with treatment group as factors and log-transformed baseline value as covariate. The log-transformed data is obtained by taking the log of the ratio of post-baseline and baseline values, i.e., log (Y/X), where Y is the post-baseline value and X is the baseline value of biomarker. The model will provide an estimate of the log ratio $\hat{c}$, which will be converted back to the ratio scale. The percent change from baseline will then be estimated based

on the estimated ratio scale, that is $[\exp(\hat{c}) - 1] \times 100\%$. The results provide an overall estimate, with corresponding CIs and p-value.

The key analysis in the MAD, Part 1, of the study is the correlation of CSF trough concentration of ISIS 814907 on Day 85 with change in CSF tau concentration from baseline to final CSF collection. ISIS 814907 dose and PK (CSF trough concentration of ISIS 814907 on Day 85) will be related to target engagement using the change in CSF total tau level from baseline to Day 85 and to each CSF collection in the Post-Treatment Period. In the LTE, Part 2, of the study a key analysis will be the correlation of CSF trough concentrations of ISIS 814907 on Day 337 with change in CSF tau concentration from baseline to final CSF collection. Additional correlations between ISIS 814907 dose or PK (CSF trough concentration of ISIS 814907 on Day 85) and changes in pharmacodynamic endpoints may be produced.

In the LTE and MAD+LTE Periods, the actual values, change, and percent change from baseline for CSF biomarkers at each visit will be summarized using descriptive statistics.

Pearson correlation coefficients and related p-value will be reported in the correlation analysis. A scatterplot will be produced to display the correlation between two quantitative variables.

All evaluated parameters will be presented in data listings.

### *3.7.2 Neuroimaging Analysis*

All MRI and PET imaging parameters will be presented in data listings for the MAD and MAD+LTE Periods, separately.

#### *3.7.2.1 Structural MRI – Volumetric Analysis*

Structural MRI analyses will be performed for the MAD, LTE, and MAD+LTE Periods.

Hippocampal volumes (left, right and total), whole brain volume, ventricular volumes (including lateral ventricle right, lateral ventricle left, 3rd ventricle, 4th ventricle, all ventricles), and baseline/screening total intracranial volume (ICV) will be assessed using MRI. The ROIs are listed in Appendix Table A1. The volumes of hippocampus, whole brain, and ventricles as a % of total intracranial volume can be calculated by: (Volume / ICV) *100. It is important to note that changes in volume may be due to atrophy or the reduction of tau neurofibrillary tangles, amyloid-beta plaques, or inflammation due to treatment (pseudo-atrophy). Volumetric analyses cannot distinguish between these possibilities.

In the MAD Period, the following results at each visit will be summarized using descriptive statistics:

- Raw results in baseline/screening Total Intracranial Volume (ICV)
- Raw results and absolute changes from baseline in whole brain volume, whole brain volume as a % of total ICV, hippocampal volumes (left, right and total), and hippocampal volumes as a % of total ICV, ventricular volumes (lateral ventricle right,

lateral ventricle left, 3rd ventricle, 4th ventricle, all ventricles), and ventricular volumes as a % of total ICV

The absolute change from baseline in whole brain volume, hippocampal volumes, ventricular volumes as listed in Table A1, and the aforementioned volumes as % of ICV will be compared between each ISIS 814907 treated analysis group and pooled placebo using the ANCOVA with baseline value and baseline age as covariates or Wilcoxon Rank Sum test, as appropriate.

In the LTE and MAD+LTE Periods, the actual values in baseline/screening ICV; the actual values and absolute changes from baseline in whole brain volume, hippocampal volumes, ventricular volumes and the aforementioned volumes as a % of total ICV will be summarized at each visit using descriptive statistics.

#### *3.7.2.2 Exploratory MRI Analyses*

##### 3.7.2.2.1 Perfusion Analysis – Arterial spin labelling (ASL)

ASL MRI will be used to quantitate changes in tissue perfusion. The measurement of cerebral blood flow (CBF) in specific regions of interest will assess if changes have occurred between baseline and subsequent imaging timepoints. We will calculate six composites: frontal, cingulate, medial temporal, temporal, parietal, and occipital. Each composite can be derived by averaging the perfusion results from the individual regions listed in Appendix Table A2 constituting the composite.

In the MAD Period, the actual values of each composite and absolute changes from baseline at Day 169 visit will be summarized using descriptive statistics. The absolute changes from baseline at Day 169 will be compared between each ISIS 814907 treated analysis group and pooled placebo using the ANCOVA with baseline value and baseline age as covariates or Wilcoxon Rank Sum test, as appropriate. In case of very few evaluable scans, only descriptive summary by visit will be provided and ANCOVA may not be performed.

In the LTE and MAD+LTE Periods, the actual values and changes from baseline at Day 449 visit will be summarized using descriptive statistics.

##### 3.7.2.2.2 Diffusion Analysis

To assess if the integrity of white matter (WM) is affected by the intervention, analysis of DTI scans will be performed. DTI allows for the identification of microscopic changes in WM tracts (e.g., demyelination) through assessing microscopic changes in water molecule mobility (diffusion). Measurements of water diffusion in WM includes mean, radial, and axial diffusivity and fractional anisotropy (FA). These measurements will be carried out within specific ROIs of the brain. The ROIs include cingulum and hippocampus left and right, forceps major (posterior forceps) and fornix as listed in Appendix Table A3.

In the MAD Period, the actual values and absolute changes from baseline at Day 169 visit will be summarized using descriptive statistics. The absolute changes from baseline at Day 169 will be compared between each ISIS 814907 treated analysis group and pooled placebo using the ANCOVA with baseline value and baseline age as covariates or Wilcoxon Rank Sum test, as appropriate.

In the LTE and MAD+LTE Periods, the actual values and changes from baseline at Day 449 visit will be summarized using descriptive statistics.

#### 3.7.2.2.3 Cortical Thickness

To assess if the intervention is affecting atrophy, the average cortical thickness will be measured in regions known to be affected by AD. T1 MRI scans will be analyzed to determine average cortical thickness (mm) for the whole brain for each patient and timepoint to assess changes with treatment and time. It is important to note that changes in cortical thickness may be due to atrophy or the reduction of tau neurofibrillary tangles, amyloid-beta plaques, or inflammation due to treatment (pseudo-atrophy). Cortical thickness analyses cannot distinguish between these possibilities.

In the MAD Period, the actual values of cortical thickness and absolute changes from baseline at Day 169 visit will be summarized using descriptive statistics. The absolute changes from baseline at Day 169 will be compared between each ISIS 814907 treated analysis group and pooled placebo using the ANCOVA with baseline value and baseline age as covariates or Wilcoxon Rank Sum test, as appropriate.

In the LTE and MAD+LTE Periods, the actual values and changes from baseline at Day 449 visit will be summarized using descriptive statistics.

#### 3.7.2.2.4 White matter lesion analysis

WM lesion analysis will measure the volume of white matter lesions relative to treatment and timepoint. A Lesion Prediction Algorithm (LPA) (Schmit P., 2016) will be implemented to estimate the white matter lesion (WML) volume.

In the MAD Period, the actual values of WML volume and absolute changes from baseline at Day 169 visit will be summarized using descriptive statistics. The absolute changes from baseline at Day 169 will be compared between each ISIS 814907 treated analysis group and pooled placebo using the ANCOVA with baseline value and baseline age as covariates or Wilcoxon Rank Sum test, as appropriate.

In the LTE and MAD+LTE Periods, the actual values and changes from baseline at Day 449 visit will be summarized using descriptive statistics.

#### 3.7.2.2.5 CSF space analysis

The CSF space in individuals will be assessed on T1 and T2 MRI of the brain and spinal cord at screening only. Total CSF space varies between individuals, and atrophy further increases the variability. Assessment of CSF will be determined for each patient on screening MRIs (Chazen et. al, 2017; De Leener et. al, 2018; Sandhya et. al, 2017). Total CSF includes both cranial CSF and spinal CSF. Thus, the total CSF volume is calculated by adding the cranial and spinal CSF volumes. The imaging of CSF space at Screening will be summarized as baseline characteristics.

### *3.7.2.3 Positron emission tomography (PET) Analysis*

This analysis will be performed on the ITT population for the MAD, LTE, and MAD+LTE Periods.

Patients will undergo FDG-PET or Tau-PET imaging to visualize brain changes. In the MAD Period, PET imaging will only be done in Cohorts C and D, and in the LTE, PET imaging will be done in all patients.

- For Cohorts C and D, PET imaging will be done 3 times over the course of the study: during the MAD screening window, at the MAD Day 169 visit, and at the Day 449 visit in the LTE.
- For patients from Cohorts A and B returning to participate in the LTE, PET imaging will be at 2 time points, during the LTE Registration Period and at the Day 449 visit in the LTE.

If Tau-PET is either not available at the site or has not yet been approved, then FDG-PET should be performed. If Tau-PET becomes available to patients in Cohorts C and D in the MAD, then patients should switch to Tau-PET if there are at least 2 imaging time points remaining to enable longitudinal analyses.

Standard uptake values (SUVs) will be extracted to calculate standard uptake value ratio (SUVR), the ratio of target region SUV to reference region SUVs. SUVR values will be computed for the target ROIs. The SUVR values of ROIs will be used to calculate six composites for FDG- or Tau-PET: frontal, cingulate, medial temporal, temporal, parietal, and occipital. Each composite can be derived by averaging the SUVR values from the individual regions listed in Appendix Table A2 constituting the composite. For Tau-PET, the composites will be obtained using the SUVRs that are calculated using cerebellum ventral as the reference region. For FDG-PET, the composites will be obtained using the SUVRs that are calculated using whole cortex, pons vermis and AD preserved as reference regions, respectively.

In the MAD Period, the actual values of each composite and absolute changes from baseline at Day 169 visit will be summarized using descriptive statistics. The absolute changes from baseline at Day 169 will be compared between each ISIS 814907 treated analysis group and pooled placebo using the using the ANCOVA with baseline value as a covariate or Wilcoxon Rank Sum test, as appropriate. In case of very few evaluable scans, only descriptive summary by visit will be provided and ANCOVA may not be performed.

In the LTE Period and MAD+LTE Period, the actual values of each composite and changes from baseline at post-baseline visit will be summarized using descriptive statistics.

FDG- and Tau- PET SUVR results of the target ROIs and the composite values will be presented in data listings for the MAD and MAD+LTE Periods.

### *3.7.3 Clinical Evaluations*

#### *3.7.3.1 Functional Activities Questionnaire (FAQ)*

FAQ is used to measure functioning/ability to perform activities of daily living.

In the MAD Period, FAQ total score (actual value, absolute change and percent change from baseline) will be summarized by treatment group and each post-baseline visit at Day 113, 169 and 253 visits using descriptive statistics. The absolute changes from baseline at each post-baseline visit will be compared between each ISIS 814907 treated analysis group and pooled placebo using the ANCOVA with baseline value as a covariate or Wilcoxon Rank Sum test, as appropriate.

In the LTE Period, the actual values, changes and percent changes from baseline at Day 449 visit will be summarized using descriptive statistics.

All FAQ collected scores will be presented in data listings for the MAD and MAD+LTE Periods.

#### *3.7.3.2 Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)*

The RBANS assessment yields five index scores, one for each of the domains tested: attention, visuospatial/constructional abilities, language, immediate memory and delayed memory.

In the MAD Period, RBANS index scores, sum of index scores and total scale (actual value, absolute change and percent change from baseline) will be summarized by treatment group and each post-baseline visit at Day 56, 113, 169 and 253 visits using descriptive statistics. The absolute changes from baseline at each post-baseline visit will be compared between each ISIS 814907 treated analysis group and pooled placebo using the ANCOVA with baseline value as a covariate or Wilcoxon Rank Sum test, as appropriate.

In the LTE Period and the MAD + LTE Periods, the actual values, changes and percent changes will be summarized by analysis group and each post-baseline visit within the Period.

All RBANS collected scores will be presented in data listings for the MAD and MAD+LTE Periods.

#### *3.7.3.3 Mini-mental State Examination (MMSE)*

The MMSE has five different domains:

- Orientation: a maximum of 10 points, calculated by adding Orientation to Time and Orientation to Place;
- Memory: a maximum of 6 points, calculated by adding Recall and Registration;

- Attention/Calculation: a maximum of 5 points;
- Language: a maximum of 8 points, calculated by adding Naming, Comprehension, Repetition, Reading and Writing;
- Visual construction: a maximum of 1 point, which is Drawing.

In the MAD Period, MMSE domain scores and total score (actual value, absolute change and percent change from baseline) will be summarized by treatment group and each post-baseline visit at Day 56, 113, 169 and 253 visits using descriptive statistics. The absolute changes from baseline at each post-baseline visit will be compared between each ISIS 814907 treated analysis group and pooled placebo using the ANCOVA with baseline value as a covariate or Wilcoxon Rank Sum test, as appropriate.

In the LTE and MAD+LTE Periods, the actual results, changes and percent changes will be summarized by analysis group and each post-baseline visit within the period.

All MMSE collected scores will be presented in data listings for the MAD and MAD+LTE Periods.

#### *3.7.3.4 Neuropsychiatric Inventory - Questionnaire (NPI-Q)*

The NPI-Q is an informant-based instrument that measures the presence and severity of 12 neuropsychiatric symptoms (e.g., anxiety, disinhibition, agitation/aggression). NPI-Q scores include Severity score (for patient) and Distress score (for caregiver). The severity scale has scores ranging from 1 to 3 points, and the scale for assessing caregiver distress has scores ranging from 0 to 5 points. Higher scores indicate more severity/distress. Total severity score is calculated as sum of severity scores for all 12 domains; and total distress score is calculated as sum of distress scores for all 12 domains.

In the MAD Period, the NPI-Q total severity score and total distress score (actual value, absolute change and percent change from baseline) will be summarized by treatment group and each post-baseline at Day 113, 169 and 253 visits using descriptive statistics. The absolute changes from baseline at each post-baseline visit will be compared between each ISIS 814907 treated analysis group and pooled placebo using the ANCOVA with baseline value as a covariate or Wilcoxon Rank Sum test, as appropriate.

In the LTE Period, the actual values, changes and percent changes will be summarized by analysis group and post-baseline visit at Day 449.

All NPI-Q collected scores will be presented in data listings for the MAD and MAD+LTE Periods.

#### *3.7.3.5 Clinical Dementia Rating (CDR) Scale*

The CDR is a global scale used at Screening to categorize the severity of Alzheimer's type dementia. It is used to rate the patient's cognitive performance in 6 domains: memory,

orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Categorical scores for each domain are 0 (none), 0.5 (questionable), 1 (mild), 2 (moderate) and 3 (severe). A summed total score (CDR Sum of Boxes [CDR-SOB]) is produced, and a global score (using the same 5 grades of dementia) is derived. CDR are collected at Screening (all cohorts), Registration/Part 2 (Cohorts A and B only) and Day 449/Part 2 (all cohorts).

In the MAD period, the CDR-SOB at Screening will be summarized as baseline characteristics.

In the LTE and MAD+LTE Periods, CDR-SOB, global score and subdomain scores (actual value, absolute change and percent change from baseline) will be summarized by analysis group and each post-baseline visit at Registration visit (for Cohorts A and B only) and at Day 449 visit.

All CDR collected scores will be presented in data listings for the MAD and MAD+LTE Periods.

# 4. REFERENCES

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# 5. APPENDIX

**Table A1: ROIs for Volumetric Analysis**

| ROI Name | ROI Description |
|---|---|
| INTRACRANIAL [a] | Total Intracranial Volume (ICV) |
| HIPPOCAMPUS_RIGHT | Hippocampus right |
| HIPPOCAMPUS_LEFT | Hippocampus left |
| HIPPOCAMPUS [*] | Hippocampus |
| VENTRICLE_LATERAL_RIGHT | Lateral Ventricle right |
| VENTRICLE_LATERAL_LEFT | Lateral Ventricle left |
| THIRD_VENTRICLE | 3rd Ventricle |
| FOURTH_VENTRICLE | 4th Ventricle |
| BRAIN_VENTRICLE [**] | All ventricles |
| WHOLE_BRAIN | Whole brain |

[a] ROI will only be calculated for baseline/screening scans
[*] Total Hippocampal Volume is calculated by adding up the volumes of Hippocampus right and Hippocampus left.
[**] Total Brain Ventricular Volume is calculated by adding up the volumes of Lateral Ventricle right, Lateral Ventricle left, 3rd Ventricle and 4th Ventricle.

**Table A2: ROIs for Perfusion and PET Analyses**

| ROI Name | ROI Description | Composite |
|---|---|---|
| FRONTAL_LOBE_MIDDLE_L | Middle frontal gyrus left | Frontal Composite |
| FRONTAL_LOBE_MIDDLE_R | Middle frontal gyrus right | |
| FRONTAL_LOBE_PRECENTRAL_L | Precentral gyrus left | |
| FRONTAL_LOBE_PRECENTRAL_R | Precentral gyrus right | |
| FRONTAL_LOBE_STRAIGHT_GYRUS_L | Straight gyrus left | |
| FRONTAL_LOBE_STRAIGHT_GYRUS_R | Straight gyrus right | |
| ORBITOFRONTAL_CORTEX_ANTERIOR_L | Anterior orbital gyrus left | |
| ORBITOFRONTAL_CORTEX_ANTERIOR_R | Anterior orbital gyrus right | |
| FRONTAL_LOBE_INFERIOR_L | Inferior frontal gyrus left | |
| FRONTAL_LOBE_INFERIOR_R | Inferior frontal gyrus right | |
| FRONTAL_LOBE_SUPERIOR_L | Superior frontal gyrus left | |
| FRONTAL_LOBE_SUPERIOR_R | Superior frontal gyrus right | |
| ORBITOFRONTAL_CORTEX_MEDIAL_L | Medial orbital gyrus left | |
| ORBITOFRONTAL_CORTEX_MEDIAL_R | Medial orbital gyrus right | |
| ORBITOFRONTAL_CORTEX_LATERAL_L | Lateral orbital gyrus left | |
| ORBITOFRONTAL_CORTEX_LATERAL_R | Lateral orbital gyrus right | |
| ORBITOFRONTAL_CORTEX_POSTERIOR_L | Posterior orbital gyrus left | |
| ORBITOFRONTAL_CORTEX_POSTERIOR_R | Posterior orbital gyrus right | |
| CINGULATE_SUBGENUAL_ANTERIOR_L | Subgenual frontal cortex left | Cingulate Composite |
| CINGULATE_SUBGENUAL_ANTERIOR_R | Subgenual frontal cortex right | |

| | | |
|---|---|---|
| SUBCALLOSAL_AREA_L | Subcallosal area left | |
| SUBCALLOSAL_AREA_R | Subcallosal area right | |
| CINGULATE_PRESUBGENUAL_ANTERIOR_L | Pre-subgenual frontal cortex left | |
| CINGULATE_PRESUBGENUAL_ANTERIOR_R | Pre-subgenual frontal cortex right | |
| CINGULATE_ANTERIOR_L | Cingulate gyrus anterior part left | |
| CINGULATE_ANTERIOR_R | Cingulate gyrus anterior part right | |
| CINGULATE_POSTERIOR_L | Gyrus cinguli posterior part left | |
| CINGULATE_POSTERIOR_R | Gyrus cinguli posterior part right | |
| HIPPOCAMPUS_L | Hippocampus left | Medial Temporal Composite |
| HIPPOCAMPUS_R | Hippocampus right | |
| TEMPORAL_LOBE_ANTERIOR_MEDIAL_L | Anterior temporal lobe medial part left | |
| TEMPORAL_LOBE_ANTERIOR_MEDIAL_R | Anterior temporal lobe medial part right | |
| TEMPORAL_LOBE_ANTERIOR_LATERAL_L | Anterior temporal lobe lateral part left | |
| TEMPORAL_LOBE_ANTERIOR_LATERAL_R | Anterior temporal lobe lateral part right | |
| PARAHIPPOCAMPAL_L | Parahippocampal and ambient gyri left | |
| PARAHIPPOCAMPAL_R | Parahippocampal and ambient gyri right | |
| TEMPORAL_LOBE_SUPERIOR_POSTERIOR_L | Superior temporal gyrus posterior part left | Temporal Composite |
| TEMPORAL_LOBE_SUPERIOR_POSTERIOR_R | Superior temporal gyrus posterior part right | |
| TEMPORAL_LOBE_MIDDLE_INFERIOR_L | Middle and inferior temporal gyrus left | |
| TEMPORAL_LOBE_MIDDLE_INFERIOR_R | Middle and inferior temporal gyrus right | |
| FUSIFORM_GYRUS_L | Fusiform gyrus left | |
| FUSIFORM_GYRUS_R | Fusiform gyrus right | |
| TEMPORAL_LOBE_POSTERIOR_L | Posterior temporal lobe left | |
| TEMPORAL_LOBE_POSTERIOR_R | Posterior temporal lobe right | |
| TEMPORAL_LOBE_SUPERIOR_ANTERIOR_L | Superior temporal gyrus anterior part left | |
| TEMPORAL_LOBE_SUPERIOR_ANTERIOR_R | Superior temporal gyrus anterior part right | |
| PARIETAL_LOBE_POSTCENTRAL_L | Postcentral gyrus left | Parietal Composite |
| PARIETAL_LOBE_POSTCENTRAL_R | Postcentral gyrus right | |
| PARIETAL_LOBE_SUPERIOR_L | Superior parietal gyrus left | |
| PARIETAL_LOBE_SUPERIOR_R | Superior parietal gyrus right | |
| PARIETAL_LOBE_INFERIORLATERAL_L | Inferiolateral remainder of parietal lobe left | |
| PARIETAL_LOBE_INFERIORLATERAL_R | Inferiolateral remainder of parietal lobe right | |
| OCCIPITAL_LOBE_LATERAL_L | Lateral remainder of occipital lobe left | Occipital Composite |
| OCCIPITAL_LOBE_LATERAL_R | Lateral remainder of occipital lobe right | |
| OCCIPITAL_LOBE_LINGUAL_GYRUS_L | Lingual gyrus left | |
| OCCIPITAL_LOBE_LINGUAL_GYRUS_R | Lingual gyrus right | |
| OCCIPITAL_LOBE_CUNEUS_L | Cuneus left | |
| OCCIPITAL_LOBE_CUNEUS_R | Cuneus right | |

**Table A3: ROIs for Diffusion Analysis**

| ROI Name | ROI Description |
|---|---|
| CINGULUM_HIPPOCAMPUS | Cingulum and hippocampus left and right |
| FORCEPS_MAJOR | Forceps major (posterior forceps) |
| FORNIX | Fornix |

**Table B1: LTE Period: Analysis Groups and Baseline Definition**

| Baseline reference [1] | Cohort | MAD period treatment | LTE period treatment [2] | Late start ABC | Late start D | Early start A | Early start B | Early start C | Early start D | ISIS 814907 60 mg Q12W [3] | ISIS 814907 115 mg Q12W | All Roll-over |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| prior to LTE | A | Placebo | ISIS 814907 60 mg q12w | X | | | | | | X | | X |
| | B | Placebo | ISIS 814907 60 mg q12w | X | | | | | | X | | X |
| | C | Placebo | ISIS 814907 60 mg q12w | X | | | | | | X | | X |
| | D | Placebo | ISIS 814907 115 mg q12w | | X | | | | | | X | X |
| prior to MAD | A | ISIS 814907 10 mg q4w | ISIS 814907 60 mg q12w | | | X | | | | X | | X |
| | B | ISIS 814907 30 mg q4w | ISIS 814907 60 mg q12w | | | | X | | | X | | X |
| | C | ISIS 814907 60 mg q4w | ISIS 814907 60 mg q12w | | | | | X | | X | | X |
| | D | ISIS 814907 115 mg q12w | ISIS 814907 115 mg q12w | | | | | | X | | X | X |

[1] Please refer to Section 3.2.2 and 3.2.3 for details and exceptional instances.
[2] As indicated by the orange highlighting, only the LTE period (and relevant baseline) data will contribute to the analysis.
[3] Select analyses only.
Note: In case of very few subjects, the analysis groups may be pooled.

**Table B2: MAD+LTE Period: Analysis Groups and Baseline Definition**

| Baseline reference [1] | Cohort | MAD period treatment [2] | LTE period treatment [2] | Late start ABC | Late start D | Early start A | Early start B | Early start C | Early start D |
|---|---|---|---|---|---|---|---|---|---|
| prior to MAD | A | Placebo | ISIS 814907 60 mg q12w | X | | | | | |
| | B | Placebo | ISIS 814907 60 mg q12w | X | | | | | |
| | C | Placebo | ISIS 814907 60 mg q12w | X | | | | | |
| | D | Placebo | ISIS 814907 115 mg q12w | | X | | | | |
| | A | ISIS 814907 10 mg q4w | ISIS 814907 60 mg q12w | | | X | | | |
| | B | ISIS 814907 30 mg q4w | ISIS 814907 60 mg q12w | | | | X | | |
| | C | ISIS 814907 60 mg q4w | ISIS 814907 60 mg q12w | | | | | X | |
| | D | ISIS 814907 115 mg q12w | ISIS 814907 115 mg q12w | | | | | | X |

[1] Please refer to Section 3.2.2 and 3.2.3 for details and exceptional instances.
[2] As indicated by the orange highlighting, data from both the MAD and LTE periods will contribute to the analysis.
Note: In case of very few subjects, the analysis groups may be pooled.

**Table B3: Active Treatment Period: Analysis Groups and Baseline Definitions**

| Baseline reference [1] | Cohort | MAD period treatment [2] | LTE period treatment [2] | Late start ABC | Late start D | Early start A | Early start B | Early start C | Early start D | ISIS 814907 115mg Q12W | Total Active |
|---|---|---|---|---|---|---|---|---|---|---|---|
| prior to LTE | A | Placebo | ISIS 814907 60 mg q12w | X | | | | | | | X |
| | B | Placebo | ISIS 814907 60 mg q12w | X | | | | | | | X |
| | C | Placebo | ISIS 814907 60 mg q12w | X | | | | | | | X |
| | D | Placebo | ISIS 814907 115 mg q12w | | X | | | | | X | X |
| prior to MAD | A | ISIS 814907 10 mg q4w | ISIS 814907 60 mg q12w | | | X | | | | | X |
| | B | ISIS 814907 30 mg q4w | ISIS 814907 60 mg q12w | | | | X | | | | X |
| | C | ISIS 814907 60 mg q4w | ISIS 814907 60 mg q12w | | | | | X | | | X |
| | D | ISIS 814907 115 mg q12w | ISIS 814907 115 mg q12w | | | | | | X | X | X |

[1] Please refer to Section 3.2.2 and 3.2.3 for details and exceptional instances.
[2] As indicated by the orange highlighting, data from periods in which a subject received active ISIS 814907 treatment (and relevant baseline data) will be included in the active treatment period analysis. Data collected during placebo dosing are not included (except relevant baseline data).
Note: In case of very few subjects, the analysis groups may be pooled.
Note: ISIS 814907 60 mg Q12W group will be included for select analyses only in the Active Treatment Period, including: serious TEAEs potentially related to Study Drug, overall summary of TEAEs, and safety MRIs.

| | |
|---|---|
| Version: | 1 |
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