Official Protocol Title:	A Parallel-Group, Double-Blind, Long Term Safety and Efficacy Trial of MK-8931 (SCH 900931) in Subjects with Amnestic Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal AD).
NCT number:	NCT01953601
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TITLE:

A Parallel-Group, Double-Blind, Long Term Safety and Efficacy Trial of MK-8931 (SCH 900931) in Subjects with Amnestic Mild Cognitive Impairment Due to Alzheimer's Disease (Prodromal AD).

This long term trial is an EXTENSION of the initial 104-week trial.

This protocol amendment is applicable only to France.

IND NUMBER: 110,186
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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0 2.1 4.2.1.2 5.1.3 7.1.2.3.1	Trial Summary Trial Design Rationale for Trial and Selected Subject Population Subject Exclusion Criteria Confirmation of Progression to Probable AD Dementia	Eligibility criteria modified to exclude subjects who progress to dementia due to AD based on investigator diagnosis in the main 104 week study from entering the long term extension study.	Results of the Phase 2/3 clinical study MK-8931-017 did not show a benefit in AD patients who initiated MK-8931 treatment in the mild to moderate dementia stage. Therefore, the balance of benefit/risk no longer supports entry of subjects with AD dementia in the extension, where active treatment may be newly initiated. Regarding continued treatment of subjects who progress to dementia later in the trial, it is not known whether initiation of treatment at the prodromal stage would provide benefit to these subjects. Therefore, despite the lack of efficacy in the 017 population of subjects with mild to moderate dementia, the sponsor believes that continued treatment of these subjects is warranted.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
3.1	Primary Objective(s) and Hypothesis(es)	Added baseline timepoint.	Clarification
1.0 2.1 5.8	Trial Summary Trial Design Beginning and End of the Trial	Added statement that study duration is 5 years from when the first subject enrolls.	Clarification
7.1.4.2 9.3	Blinding/Unblinding Clinical Supplies Disclosure	Updated text to provide clarity around emergency unblinding procedures. Updated text to describe who may be unblinded following emergency unblinding.	Clarification

1.0 TRIAL SUMMARY

Abbreviated Title	A Long Term Safety and Efficacy Trial of MK-8931 (SCH 900931) in Subjects with Prodromal AD (APECS)
Trial Phase	III
Clinical Indication	Treatment of early (prodromal) AD
Trial Type	Interventional
Type of control	Not Applicable
Route of administration	Oral
Trial Blinding	Double-blind
Treatment Groups	MK-8931 12 mg MK-8931 40 mg
Number of trial subjects	All subjects who complete the initial 104 week trial and are willing and qualified to participate in the long term trial will be enrolled. Subjects who progress to dementia due to AD in the main 104 week study will not be permitted to move into the long term extension study. The actual number enrolled may vary depending on the number enrolled in the 104 week trial, the dropout rate, and the number of eligible subjects who consent to enroll. Based on the current sample size projection and estimated dropout rate (25%) for the initial 104 week trial, approximately 912 subjects would be enrolled. The total number of subjects enrolled in the extension will not exceed the total enrolled in the initial 104 week trial.
Estimated duration of trial	The duration of the long-term trial is expected to be up to approximately five years or until a) MK-8931 becomes commercially available (locally), or b) when the MK-8931 program is terminated (whichever comes first). Duration of the trial may be limited based on local regulation.
Duration of Participation	Expected maximum duration of no longer than 260 weeks (5 years after the first subject enrolls), with the duration of individual subject participation dependent on the timing of enrollment. Duration of participation may be limited based on local regulations. Subjects who do not complete the initial 104-week trial of MK-8931 protocol 019 will not be permitted to continue in this trial. In addition, subjects who are less than 75% compliant with trial medication during the initial 104-week trial will require Sponsor approval to participate in this trial. Subjects will be followed for at least 14 days following cessation of treatment.
Randomization Ratio	Not applicable to this trial.

A list of abbreviations used in this document can be found in Section 12.4.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a long-term safety and efficacy study (up to 260 weeks) which will be available to subjects who have completed the initial 104-week trial of MK-8931-019.

The initial 104-week trial is a double blind, randomized, parallel group, placebo controlled, multicenter trial in subjects with amnestic mild cognitive impairment (aMCI) due to Alzheimer's Disease (AD), referred to herein as prodromal AD. The initial 104-week trial, detailed in a separate amendment, includes two active dose arms of MK-8931 (12 mg and 40 mg) and placebo. Duration of treatment is 104 weeks (24 months). MK-8931 is a potent β-site APP cleaving enzyme 1 (BACE1) inhibitor being developed for the treatment of AD. The initial 104-week trial will enroll subjects who meet criteria for prodromal AD, which is defined as subjects who have aMCI and are positive for an AD biomarker. The primary AD biomarker to be used for the inclusion criterion is cortical amyloid load measured with positron emission tomography (PET).

At the end of the 104-week trial, subjects who have completed treatment and satisfy eligibility criteria may choose to participate in this trial, during which all subjects who received placebo during the initial 104-week trial will receive active drug. Subjects who progress to dementia due to AD in the main 104 week study will not be permitted to move into the long term extension study.

This trial will start with enrollment of the first subject who completes the initial 104-week trial and chooses to participate in the long term trial. The long term safety and efficacy trial will end 5 years after the first subject enrolls (260 weeks), or a) when the drug either becomes commercially available (locally), or b) when the MK-8931 program is terminated (whichever comes first). The duration of the trial may be even shorter for subjects in particular regions, per local regulation.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

This trial will use an independent, external Data Monitoring Committee (eDMC) to monitor safety at the appropriate frequency and for the duration required per the eDMC Charter.

2.2 Trial Diagram

The trial design is depicted in Figure 1.

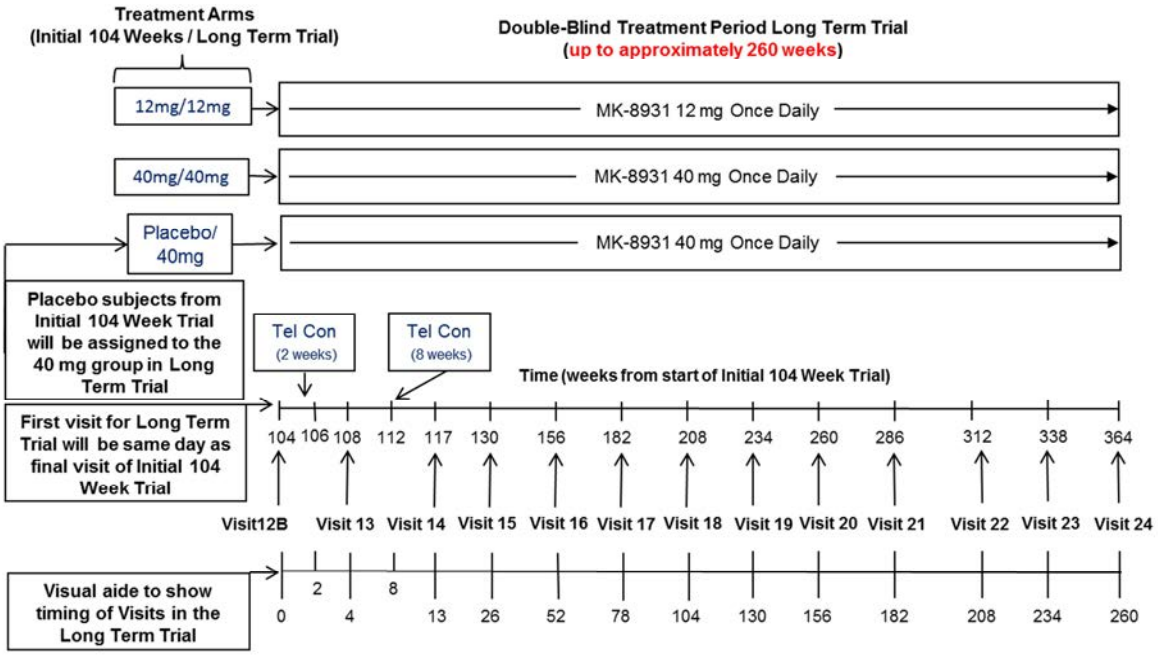

Figure 1 Trial Design Diagram

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

The two primary objectives are as follows:

1. To evaluate the safety and tolerability of MK-8931 in the long term treatment of prodromal Alzheimer's Disease (AD).

2. To compare the efficacy of MK-8931 administered to subjects for 30 months to that of subjects administered placebo for 24 months followed by MK-8931 for 6 months using the change from baseline score CDR-SB score at Week 130.

For both of the primary objectives, subjects who received MK-8931 in the initial 104-week study will be compared to subjects who received placebo during that period (i.e. 40 mg / 40 mg vs. pbo / 40 mg and 12 mg / 12 mg vs. pbo. /40 mg). It is noted that baseline refers to the baseline from the initial 104-week trial.

3.2 Secondary Objective(s) & Hypothesis(es)

There are no secondary objectives or hypotheses for this long-term extension.

3.3 Other Objectives (e.g., Tertiary, Exploratory, etc.)

Objectives:

To compare the efficacy of MK-8931 administered to subjects for 24 months followed by long term treatment of MK-8931 to that of subjects administered placebo for 24 months followed by long term treatment of MK-8931 on

1) cognition, function, disease progression, and health economic burden at multiple time points.

2) time to progression to probable AD dementia as determined by investigator-diagnosis.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB) for detailed background information on MK-8931.

4.1.1 Pharmaceutical and Therapeutic Background

Alzheimer's Disease (AD) is a slowly developing neurodegenerative disease that is the leading cause of dementia world-wide. Currently available treatments for AD are limited, and include acetylcholinesterase inhibitors (e.g., donepezil) and the low affinity N-methyl D-aspartate (NMDA) receptor antagonist (memantine). These medicines modestly improve symptoms but do not alter disease progression. Therefore, novel pharmacological agents that slow or halt the progression of AD are needed.

Alzheimer's Disease is characterized by specific histopathological features including amyloid deposits (plaques), neurofibrillary tangles, and neuronal degeneration. The "amyloid hypothesis" posits that amyloid β (Aβ) peptides aggregate into complexes, such as fibrils and plaques, which subsequently trigger the development of tau-related neurofibrillary tangles. These tangles are thought to be the more proximal cause of neuronal degeneration. Aβ pathology appears to begin years before the onset of AD dementia and is thought at some point to trigger tau pathology, neural degeneration, and the subsequent gradual emergence of clinical symptoms. As amyloid plaques continue to accumulate, tangle pathology spreads to a variety of brain regions, leading to progressive neuronal degeneration, brain atrophy, and cognitive decline. As a result, early intervention to reduce Aβ accumulation when patients are in the prodromal phase, or even earlier, has gained increasing acceptance as a promising approach to reduce the incidence of AD.

Aβ peptides are produced when amyloid precursor protein (APP) is cleaved by three distinct proteases: α secretase, BACE1 (β site APP cleaving enzyme 1, also known as β-secretase), and γ secretase. Most APP is processed by α and γ secretases to generate nonamyloidogenic peptides. However, 5-10% of APP is cleaved by BACE1 and γ secretase to generate pathogenic Aβ peptides (Aβ40 and Aβ42). Deletion of BACE1 in mice eliminates Aβ in

both the plasma and the brain. Thus, inhibition of BACE1 is a potential therapeutic strategy for slowing or halting progression of AD.

MK-8931 is a potent BACE1 inhibitor being developed for the treatment of AD. It has been shown to reduce Aβ levels in the CSF and brain of rodents and primates. MK-8931 also reduces Aβ in human CSF. In Phase 1 trials, MK-8931 has been generally safe and well tolerated (see IB). These results suggest that MK-8931 may reduce Aβ production in humans and could potentially slow progression in subjects with prodromal AD.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

4.2.1.1 Trial Design Rationale

This is a parallel group, multi-site, double-blind, long term safety and efficacy trial to provide access to MK-8931 before it is commercially available, to estimate the effects of delayed start of MK-8931, and to evaluate the safety and tolerability of two doses of MK-8931 in extended treatment of prodromal AD. MK-8931 is hypothesized to exert disease-modifying effects in subjects with prodromal AD. A delayed-start design may provide supportive evidence of disease modification in prodromal AD if the treatment effect is sustained and greater in the group of subjects that starts the active treatment earlier as compared to the group of subjects with a substantial delay in start of active treatment. Results from this long term trial will also provide data regarding the sample size necessary for delayed start studies with disease modifying therapeutics for AD. In addition, this long term trial will be used to further assess the long term effects of MK-8931 on disease progression, health economic effects and the safety and tolerability of MK-8931. Some Sponsor personnel will be unblinded following the completion of the initial 104-week trial. A separate group of Sponsor personnel will remain blinded during the long-term trial, in order to ensure the proper conduct of the trial in furtherance of the collection of quality efficacy data, including the 30-month timepoint to support the primary objective regarding efficacy. Details are included in the Sponsor's blinding document.

4.2.1.2 Rationale for Subject Population and Dose

The recent results from Protocol 017 indicate that MK-8931 is not effective when treatment is initiated in subjects with mild/moderate AD. The amyloid hypothesis suggests, however, that earlier treatment with a BACE inhibitor (prior to the onset of dementia) could be beneficial even if ineffective at later stages. The initial 104-week trial of Protocol 019 in prodromal AD is still ongoing so the impact of BACE inhibition in this earlier stage of the disease is not yet known. Given this uncertainty along with the 017 results, subjects who tolerated study medication, have not progressed to dementia and completed the initial 104-week trial of Protocol 019 may enroll in this long term trial. However, subjects who have progressed to dementia will be excluded since the 017 results indicate increased adverse events in addition to no efficacy.

Subjects in the initial 104 week trial who progress to dementia during that time have a 2 out of 3 chance of being on active treatment with MK-8931. Based on the view that these subjects could still benefit from MK-8931 since it was initiated before the onset of dementia, one alternative is to allow these subjects into the extension trial. However, since the blind will be maintained in the extension, it is not possible to include these subjects while excluding subjects who were on placebo during the initial 104-week trial. Given the concern that the placebo treated subjects who progress to dementia would not benefit from treatment, the current protocol will exclude all subjects who have progressed to dementia.

Subjects who progress to dementia during this extension trial will be allowed to continue, since it is not known whether initiation of treatment at the prodromal stage would provide benefit to these subjects. Therefore, despite the lack of efficacy in the 017 population where treatment was initiated at the mild to moderate dementia stage, the sponsor believes that continued treatment of these subjects is warranted.

Those subjects who did not complete treatment in the initial 104-week trial, but continued with and completed scheduled visits may be permitted to enroll in this long term trial based on the discretion of the Sponsor. Where required locally by IRBs/ECs (including sites in France), these subjects may enroll in the long term trial without Sponsor approval. Subjects who received the 12 mg or 40 mg dose during the 104-week trial will continue to receive the same dose in this long term trial. They will be referred to as the 12/12 and 40/40 groups respectively. Subjects who received placebo during the initial 104-week trial will receive the 40 mg dose during this long term trial. They will be referred to as the placebo/40 group.

The 40-mg dose has been shown to substantially inhibit CSF Aβ. The 12-mg dose produces a more moderate reduction in CSF Aβ and is included since the long term safety of greater inhibition is unknown. Using PK/PD modeling and simulation, 12-mg and 40-mg doses are projected to reduce CSF Aβ by at least 50% and 75%, respectively, in more than 90% of subjects. It is unknown how much Aβ lowering is optimal from the perspective of both safety/tolerability as well as efficacy. Subjects who received placebo during the initial 104-week trial will be treated with the 40-mg dose in the long term trial to provide additional information about the long term safety of 40 mg of MK-8931 and to estimate the clinical effects of delayed start of this higher dose.

4.2.2 Rationale for Endpoints

4.2.2.1 Outcome Measures Rationale

As in the protocol for the initial 104-week trial, the primary outcome measure is the change from Baseline in the Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) score at 130 weeks. The CDR-SB is highly relevant clinically and has been shown to worsen over time in this patient population.

Progression to probable AD dementia will be included in the long term trial as an exploratory objective. This study will use both NINCDS ARDRA and Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria to define probable AD dementia. Unlike the initial 104-week trial, cases of progression in the long term trial

will not be reviewed by an adjudication committee; therefore, the final decision on progression will be the opinion of the investigator or qualified designee. The progression endpoint will provide useful information for patients and physicians for understanding the effects of MK-8931.

Other clinical measures include the following: a) the composite cognition score (based on the mean of the three domain z-scores from tests of episodic memory, working memory/executive function, and attention/psychomotor speed) and b) the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS ADL_{MCI}) (mild cognitive impairment [MCI] version) score. Previously conducted trials have demonstrated that cognition and function are relevant dimensions of clinical progression in this patient population. Regarding cognition, prior studies of MCI have used some version of the Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-Cog). Because of the well-known issue with sensitivity of the ADAS-Cog, many studies have also included additional, standard cognitive tests. Several methods have been proposed to combine the ADAS-Cog with the additional tests to generate a composite cognition score. While intensive ongoing research may clarify the optimal approach, this protocol will calculate the average z-score of three cognitive domains thought to be involved in prodromal AD based on modeling suggesting this is superior to the ADAS-Cog alone.

Additional clinical endpoints include scores from the 13-item ADAS-Cog with Delayed Word Recall and Number Cancellation tasks (ADAS Cog13), the Mini Mental State Examination (MMSE), the Neuropsychiatric Inventory (NPI), cognitive and functional subscales of the CDR-SB, and the Health Economic Outcomes (HEA, RUD lite, EQ-5D).

4.2.2.2 Safety Measures Rationale

Safety and tolerability will be assessed by clinical review of AEs, laboratory tests, vital signs, and ECG measurements. The same safety parameters and AEs designated as being of special interest during the initial 104-week trial will continue to be monitored in the long term trial, including delirium, and rash ECI (see Section 7.2.3.2).

Regarding MRI monitoring, the US FDA had noted the occurrence of imaging abnormalities believed to represent cerebral vasogenic edema in association with the investigational use of Aβ antibodies that are intended to treat AD by reducing β-amyloid in the brain. These imaging abnormalities, described in Salloway et al [36], have, in the majority of instances, been asymptomatic and their presence has been detected by routine MRI scans. Symptoms, when present, include headache, worsening of cognitive function, alteration of consciousness, seizures, unsteadiness, and vomiting. In most instances, the occurrence of such imaging abnormalities, even when symptomatic, has not required treatment beyond discontinuation of the investigational compound; infrequently, high-dose steroid therapy has been administered in the presence of prominent symptoms. Previous regulatory guidance required that all subjects have an MRI scan during Screening in order to qualify for the trial and routine MRI scans for safety monitoring. Following a comprehensive review of the existing data, the FDA has updated this guidance stating that serial clinical and MRI monitoring will no longer be required as a matter of course in clinical trials of small molecule

drugs that may affect β-amyloid. Therefore, routine MRI safety monitoring is not included in this trial. MRIs may be performed for safety monitoring if clinically indicated as determined by the investigator (e.g., in follow up to an AE).

After initiation of the initial 104-week trial, the FDA issued guidance to sponsors indicating that all trials with BACE1 inhibitors that are longer than two weeks in duration must include routine monitoring of skin. Therefore, in order to gain additional data on those previously not exposed to MK-8931 during the initial 104-week trial, i.e. those subjects on placebo, routine skin examinations by a site physician will continue in this study. If no difference is seen in the occurrence of hypopigmentation between the placebo and MK-8931 groups after 300 subjects/group are evaluated at six months in the MK-8931 program (P017 and P019), the eDMC may recommend the discontinuation of the routine skin examinations. Sites would continue to collect skin-related adverse events and refer subjects for further dermatologic evaluation as needed.

4.2.2.3 Planned Biomarker Research

As noted in the IB, rash has been observed in Phase I studies and may be a risk for patients who take MK-8931. Preliminary results from Phase I studies suggest that rash may be associated with specific HLA genotypes. To explore this issue further, DNA was collected from all subjects in the initial 104-week study and stored for HLA genotyping if indicated. HLA genotyping will be performed on subjects who develop a rash in this trial and a matched control group who do not develop rash.

4.2.2.4 Future Biomedical Research

Some subjects in the initial 104-week study gave consent for using specimens for future biomedical research. These included blood for genomics use, and CSF (in the optional CSF sub study). Phenotypes generated from the current long term extension study may also be used in conjunction with biomedical specimens for research.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects who completed the initial 104-week trial.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Have tolerated study medication and completed the initial 104-week trial. Subjects who did not complete the initial 104-weeks of treatment but continued with and completed scheduled visits may be permitted to continue in the long term extension at the discretion of the Sponsor. Subjects who repeatedly deviate from protocol requirements will not be permitted to continue in this extension. In addition, subjects who are less than 75% compliant with trial medication during the initial 104-week trial will not be permitted to continue in the long term extension, except in special circumstances, which require Sponsor approval (or, where required locally, approval of the investigator rather than the Sponsor).

2. Have a trial partner who is reliable and competent. The trial partner must have a close relationship with the subject, have face to face contact at least 3 days/week for a minimum of 6 waking hours/week (or more, based on local requirements), be willing to accompany the subject to all trial visits, and be willing to monitor compliance of the administration of the trial medication. The trial partner should understand the nature of the trial and adhere to trial requirements (e.g. dose, visit scheduled and evaluations). It is recommended that the trial partner accompany the subject to all trial visits.

3. Sign (or legal representative signature) the informed consent in accordance with local requirements, after the scope and nature of the trial have been explained.

4. Agree to inform their general practitioner of their participation in this study.

   Note: PI will follow up with subject to ensure compliance and document notification of the general practitioner in subjects medical records.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Has progressed to dementia due to AD per investigator diagnosis in the initial 104-week study.

2. Is in imminent risk of self harm, based on clinical interview or on the Columbia Suicidality Severity Rating Scale (C-SSRS), or of harm to others in the opinion of the investigator. Subjects who report suicidal ideation with intent, with or without a plan (e.g., suicidal ideation item 4 or 5 on the C-SSRS) in the past one (1) month or suicidal behavior in the past six (6) months should be excluded. Such subjects will be permitted to rescreen for entry into this study once in the Investigator's opinion, this risk of harm to self or others is no longer present.

3. Has developed a recent or ongoing, uncontrolled, clinically significant medical or psychiatric condition that precludes participation in this protocol in the judgment of the investigator.

4. Based on results from the EOT Visit (Visit 12) in the initial 104-week trial has results of clinical laboratory tests (complete blood count [CBC], blood chemistries, and urinalysis) that are clinically unacceptable to the investigator. However, it is recognized that lab results will not be available at Visit 12/12B if they occur on the same day. Therefore, such subjects may be enrolled prior to receiving these results; upon their receipt of the lab results, if the PI feels they are clinically unacceptable the subject should be discontinued.

5. Based on the results from the EOT Visit (Visit 12) has results of a physical examination, and vital signs that are clinically unacceptable to the investigator.

6. Has developed a form of dementia that is not Alzheimer's Disease, including but not limited to, dementia due to HIV infection, head trauma, vascular disease, Parkinson's disease, frontotemporal dementia, or Huntington's disease, as determined by the investigator.

7. Anticipates receiving any of the treatments listed in Table 1 during the current trial.

Table 1 Prohibited Medications

Prohibited Medications, Supplements, and Other Substances
Anti-amyloid agents (e.g., tarenflurbil, tramiprosate)
Anti-amyloid antibodies (e.g., solanezumab)
Anti-amyloid vaccine (Subjects who received placebo only in a vaccine trial may participate in this trial.)
CYP3A4 inducers (strong) including: Rifampicin and St. John's Wort, phenytoin, carbamazepine Exceptions: Use of the following is acceptable: topical use; short-term (<2 weeks) oral treatment during the trial; use of oral St. John's Wort <300 mg three times a day during the trial, regardless of duration.

NOTE: This is not a complete list of excluded medications. Contact the Sponsor if there is a question about a specific medication.

7. Has progressed to dementia due to AD per investigator diagnosis in the initial 104-week study.

5.2 Trial Treatments

The treatments to be used in this trial are outlined below in Table 2.

Table 2 Trial Treatments

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
MK-8931	12 mg tablet	Once daily	Oral	Up to 260 weeks	Investigational
MK-8931	40 mg tablet	Once daily	Oral	Up to 260 weeks	Investigational

Subjects who received the 12 mg or 40 mg dose in the initial 104-week trial will continue to receive the same dose in this long term trial. Subjects who received placebo during the initial 104-week trial will receive the 40 mg dose during this long term trial.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.2 Timing of Dose Administration

The trial medication should be administered by the subject, by the subject's trial partner, or by a caregiver. Each subject should take one tablet at approximately the same time each day without regard to food. For each treatment group, one tablet equals one dose of trial medication as summarized below:

- 12/12 group: MK-8931 12 mg (one tablet)
- 40/40 and placebo/40 groups: MK-8931 40 mg (one tablet)

If a subject misses a dose, the subject may take the dose later in the day and should continue with the regular dosing schedule by taking the next dose at the usual time the next day. Any changes in dosing schedule should be noted by the subject or subject's trial partner and recorded by the site at the next visit. Subjects should not take more than one dose on the same calendar day.

With the exceptions of any subjects enrolled to a dose that is dropped for reasons of safety or tolerability, there will be no adjustments to the dose of any subject in the trial.

5.2.3 Trial Blinding/Masking

A double-blind/masking technique will be used. MK-8931 12 and 40 mg tablets will be packaged identically so that treatment blind/masking is maintained for the subject and the investigator. The Sponsor will be unblinded at the completion of the initial 104-week trial.

See Section 7.1.4.2, Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

5.3 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. Listed below are some specific restrictions for concomitant therapy or vaccination during the course of the trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the local Clinical Monitor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

5.3.1 Prohibited Medications

The subject must not take the treatments listed in Table 1 during this trial.

During the trial, initiation of treatment with medications known to be associated with substantial increased risk of Stevens-Johnson Syndrome or toxic epidermal necrolysis should be avoided when possible. Subjects who have been safely treated with at least one routine course of treatment with these medications in the past are exempted from this requirement. Examples of such medications are included below. The Sponsor should be consulted for questions about specific medications.

- trimethoprim-sulfamethoxazole, azithromycin, allopurinol, phenobarbital, oxicam NSAIDS (e.g., celecoxib, valdecoxib, meloxicam), carbamazepine, phenytoin, valproic acid, nevirapine, lamotrigine, and chlormezanone

5.3.2 Allowed Medications

Medications, supplements, and other substances allowed during the trial include, but are not limited to, those listed in Table 3. Note that the use of any concomitant medication must relate to the documented medical history, prophylaxis, or an adverse event of the subject. **Initiation and change of dose of cholinesterase inhibitors and memantine are allowed in this trial.**

Table 3 Medications, Supplements, and Other Substances Allowed During the Trial

Allowed Medications, Supplements, and Other Substances
Acetylcholinesterase inhibitors (e.g., donepezil, tacrine, rivastigmine, galantamine)
Memantine
Huperzine A
Vitamin E
Herbal supplements from *Ginkgo biloba*, ginseng, *Huperzia serrata* (Qian Ceng Ta)
Medical foods/supplements (e.g., Axona®, Souvenaid®)
Estrogens and estrogen-like compounds
Antihypertensives
Nonsteroidal anti-inflammatory drugs (NSAIDs)
Cycloxygenase 2 inhibitors
Neuroleptics
Antidepressants
Carbidopa/levodopa and dopamine agonists
Pregabalin and gabapentin
Rifampicin and St. John's Wort: Topical use, short-term (<2 weeks) oral treatment during the trial, use of oral St. John's Wort <300 mg three times a day during the trial, regardless of duration.
Selective H1 blockers, selective H2 blockers, and topical anti-pruritic treatments for treatment of rash during the trial, as specified in the Rash Guidance Document.

5.4 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

5.5 Diet/Activity/Other Considerations

Subjects who are provided non-pharmacological treatments, such as day care, may continue these through the trial. The frequency should not change unless medically indicated. Day care attendance on the day before clinic visits and cognitive testing should remain stable through the protocol.

5.6 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details

regarding discontinuation or withdrawal procedures are provided in Section 7.1.4 – Other Procedures.

In this trial, a subject may temporarily discontinue from treatment under certain conditions specified in the protocol (e.g. in follow-up to imaging abnormalities or rash; refer to Sections 7.1.2.2.6 and Rash Guidance Document for details) but continue to participate in the regularly scheduled activities, as long as the subject does not withdraw consent. Given the exploratory nature of this long term trial's endpoints, subjects who permanently discontinue from treatment will be discontinued from the trial.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk through continued participation in the trial or does not allow the subject to adhere to the requirements of the protocol.

A subject must be discontinued from treatment (but may continue to be monitored in the trial) for any of the following reasons:

- Elevated ALT, AST, or T-BIL meeting any one of the following criteria:
    - ALT or AST ≥ 8 x ULN;
    - ALT or AST ≥ 5 and < 8 x ULN for more than 2 weeks;
    - ALT or AST ≥ 3 x ULN and T BIL ≥ 2 x ULN at the same visit;
    - ALT or AST ≥ 3 x ULN with the appearance of symptoms indicating hepatitis (e.g., worsening fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia).

  Exception: If elevations are determined to be due to some other medical condition, subject may resume trial medication with Sponsor approval.
- An imaging abnormality consistent with intraparenchymal macrohemorrhage appears (see details in Section 7.1.2.2.6);
- QTc prolongation (defined as QTc interval > 500 ms or QTc change from baseline > 60 ms, based on the average of three measurements using the Fridericia formula for correction).
- Exception: If QTc change from baseline (from Visit 1 of the initial 104-week trial) > 60 ms is determined to be due to some other medical condition, or if subject has a new onset of bundle branch block, subject may continue treatment with Sponsor approval.

- The subject develops a form of dementia that is not Alzheimer's Disease, including but not limited to dementia due to HIV infection, head trauma, vascular disease, Parkinson's disease, frontotemporal dementia, or Huntington's disease, as determined by the investigator.

- The subject develops a severe rash confirmed by a dermatologist. For the purpose of this program, a "**severe rash**" is defined as one of the following:

    - A vesicular rash (i.e., one with blistering lesions) that is not clearly caused by herpes simplex virus or contact allergy such as poison ivy AND has EITHER a) extensive body surface area (BSA) involvement OR b) involves oral/mucosal surfaces.
    - Stevens Johnson Syndrome, erythroderma, or toxic epidermal necrolysis
    - DRESS Syndrome.

- The subject develops an uncontrolled AND clinically significant rash defined as follows:

    - A clinically significant rash (see Section 7.2.3.2) that is not controlled by topical medications or oral medications such as antihistamines (detailed in the Rash Guidance Document) AND causes intolerable symptoms attributed to study drug.

- The subject's trial partner is no longer willing or able to participate in the study and a suitable replacement trial partner cannot be found in a reasonable period of time.

5.7 Subject Replacement Strategy

A subject that discontinues from the trial will not be replaced.

5.8 Beginning and End of the Trial

Each subject is considered to be enrolled when the subject (or the subject's legal representative) has provided written informed consent in accordance with local requirements.

This long-term trial will start with enrollment of the first subject who completes the initial 104-week trial and chooses to participate in the long term trial. This trial will end after 5 years after the first subject enrolls (260 weeks), or a) when the drug either becomes commercially available (locally), or b) when the MK-8931 program is terminated (whichever comes first). Duration of participation may also be limited based on local regulations. Each subject is considered to have ended participation in the trial when he/she has completed the last protocol-specified contact (e.g., visits or telephone contacts) or has prematurely discontinued from the trial. A subject will be considered a completer of this long-term trial if he/she is still continuing in the trial when the trial is stopped.

A subject is considered to have discontinued after he/she has withdrawn consent or has been discontinued under the conditions specified in Section 7.1.4.1. Given the exploratory nature of the long-term trial, the retrieved dropout approach employed in the initial 104-week trial will be discontinued from this trial. All applicable activities scheduled for the final trial visit should be performed at the time of treatment discontinuation as defined in the long-term trial Flow Chart in Section 6.0.

A subject is considered to have been lost to follow-up if he/she is unable to be contacted by the investigator. The end of participation for a subject lost to follow-up is the last known contact (e.g., visit or telephone contact).

5.9 Clinical Criteria for Early Trial Termination

This trial may be terminated early by eDMC for safety concerns or based on the results of the interim efficacy analysis for futility of the initial 104-week trial (See section 8.1.4).

The clinical trial may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable. In addition, further recruitment in the trial or at a particular trial site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

6.0 TRIAL FLOW CHART

NOTE: Subject participation in the long term trial (Part II) is optional and will only be conducted where approved by local authorities.

Extension Trial Period:	Treatment																	
Visit Number (counting from the initial 104-week trial; Part I)	**12B[b]**	**TC[d]**	**13**	**TC[d]**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**TC[f]**	**UV**	**ETV**
Scheduled Week [a] (based on date of randomization in initial 104-week trial; Part I)	**104**	**106**	**108**	**112**	**117**	**130**	**156**	**182**	**208**	**234**	**260**	**286**	**312**	**338**	**364**			
Visit Window (Weeks)		**±1**	**±1**	**±1**	**±1**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**			
Administrative Procedures																		
Informed Consent	X																	
Collect Subject Identification Card															X			
Inclusion/Exclusion Criteria	X																	
Record Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[e]	X
Clinical Procedures/ Assessments																		
Vital Signs[c]			X		X	X	X	X	X	X	X	X		X	X		X[e]	X
Body Weight			X		X	X	X		X		X				X		X[e]	X
Directed Physical & Neurological Examinations							X		X		X		X		X		X[e]	X
Directed Skin Examination by Site Physician						X	X		X		X		X		X		X[e]	X
12-Lead Electrocardiogram			X														X[e]	
CDR						X	X		X		X		X		X			X
ADAS-Cog (13-item)					X	X	X		X		X		X		X			X
Cognition Battery																		
COWAT					X	X	X		X		X		X		X			X
Trial Making Test (A & B)					X	X	X		X		X		X		X			X
CERAD Verbal Fluency					X	X	X		X		X		X		X			X
Digit Span Test					X	X	X		X		X		X		X			X
Digit Symbol-Coding (DSC)					X	X	X		X		X		X		X			X
ADCS-ADL_{MCI}					X	X	X		X		X		X		X			X
MMSE						X	X		X		X		X		X			X
C-SSRS: Since Last Visit			X		X	X	X	X	X	X	X	X	X	X	X		X[e]	X
NPI						X	X		X		X		X		X			X

Extension Trial Period:	Treatment																	
Visit Number (counting from the initial 104-week trial; Part I)	**12B[b]**	**TC[d]**	**13**	**TC[d]**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**TC[f]**	**UV**	**ETV**
Scheduled Week [a] (based on date of randomization in initial 104-week trial; Part I)	**104**	**106**	**108**	**112**	**117**	**130**	**156**	**182**	**208**	**234**	**260**	**286**	**312**	**338**	**364**			
Visit Window (Weeks)		**±1**	**±1**	**±1**	**±1**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**			
Modified RUD Lite: Follow-Up						X	X		X		X		X		X			X
HEA						X	X		X		X		X		X			X
EQ-5D						X	X		X		X		X		X			X
CAM	X------To be completed only for adverse events of delirium----------																	
Structural MRI																	X[e]	
Monitor for Progression to Dementia[h]	X		X		X	X	X	X	X	X	X	X	X	X	X		X	X
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Procedures/ Assessments																		
Hematology and Chemistry Blood Samples[c]			X		X	X	X		X		X		X		X		X[e]	X
Urinalysis[c]			X		X	X	X		X		X		X		X		X[e]	X
Trial Medication Procedures																		
Dispense Trial Medication	X		X		X	X	X	X	X	X	X	X	X	X			X[g]	
Medication Compliance		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Drug Accountability Assessment			X		X	X	X	X	X	X	X	X	X	X	X		X	X

Extension Trial Period:	Treatment																	
Visit Number (counting from the initial 104-week trial; Part I)	**12B[b]**	**TC[d]**	**13**	**TC[d]**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**TC[f]**	**UV**	**ETV**
Scheduled Week [a] (based on date of randomization in initial 104-week trial; Part I)	**104**	**106**	**108**	**112**	**117**	**130**	**156**	**182**	**208**	**234**	**260**	**286**	**312**	**338**	**364**			
Visit Window (Weeks)		**±1**	**±1**	**±1**	**±1**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**			

ADAS-Cog = Alzheimer's Disease Assessment Scale Cognitive subscale (modified: 13-item with delayed memory recall and number cancellation tasks); ADCS-ADLMCI= Alzheimer's Disease Cooperative Study Activities of Daily Living (MCI Version); AE = Adverse Event; CAM = Confusion Assessment Method; CDR = Clinical Dementia Rating; COWAT = Controlled Oral Word Association Test; C-SSRS = Columbia Suicide Severity Rating Scale; DSC = Digit Symbol-Coding; EQ-5D = EuroQoL Five Dimension Questionnaire; ETV = Early Termination Visit; HEA = Health Economic Assessment; MCI = Mild Cognitive Impairment; MMSE = Mini-Mental State
Examination; MRI = magnetic resonance imaging; NPI = Neuropsychiatric Inventory; RUD Lite Resource Utilization in Dementia Lite Questionnaire; TC = telephone call; UV = Unscheduled Visit

a. Visits scheduled during the long term trial (Part II) will be based off of the date of randomization in the initial 104-week trial (Part I). The timing of each visit is relative to Study Day 1 of that subject with Study Day 1 defined as the date of randomization into the initial 104-week trial (which should also be the date of the first administration of trial medication in the initial 104-week trial). However, if a subject enters the extension trial at a different time point than visit 12, i.e. V12 and V12B occur on different days, subsequent visits should be based on the date V12B actually occurred and not the date of randomization.

b. Visit 12 from Part I and Visit 12B from Part II are considered a single visit and can be conducted on the same day. Subjects with a gap in therapy of > 4weeks may be allowed to continue if reason for the delay was due to, for example, HA/IRB approval, etc. If there is a a gap in study therapy >3 months the sponsor should be consulted. It is recognized that lab results will not be available at Visit 12/12B if they occur on the same day. Therefore, such subjects may be enrolled prior to receiving these results; upon their receipt, if the PI feels they are clinically unacceptable the subject should be discontinued.

c. Vital Signs and laboratory samples should be collected for subjects with > 3 month gap in therapy between visit 12 and 12B.

d. Telephone contact with subject and trial partner/caregiver by site to assess safety, AEs, concomitant medications, medication compliance, and any other issues. Any telephone contact may be conducted as an in-person unscheduled visit if the subject or caregiver expresses a preference for this or of the site has significant safety/tolerability concerns.

e. Procedures may be performed if clinically indicated as determined by the investigator.

f. Telephone contact will be performed to assess for adverse events that may have occurred up to 14 days (+ 1-week) following cessation of study medication.

g. Drug dispensing may be performed at unscheduled visits at the discretion of the Investigator.

h. Progression to dementia should be evaluated at all visits during the long term trial until the investigator or qualified designee considers the subject as having progressed to dementia (AD or non-AD). Cases of progression in this trial will not be reviewed by an adjudication committee; therefore the final decision on progression will be the opinion of the investigator or qualified designee. Note: Subjects who were confirmed to have progressed to AD dementia by the adjudication committee in the initial 104-week trial may not continue in this trial. For those subjects for whom the adjudication committee rendered a decision of non-AD dementia, the subject may continue in this trial if in the investigator's opinion the subject did not progress to AD or non-AD dementia during the initial 104-week trial.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

Given the trial population and the duration of the study, it is possible that a subject's cognition may decline to a point where they no longer have capacity to provide informed consent. If this occurs, the site should obtain consent to continue in the trial from the subject's legally acceptable representative and **in accordance with local standards and requirements**. The subject's assent to continue should also be obtained. In Germany only, due to more restrictive regulations, subjects who progress to the point where they are judged to be unable to give informed consent must be discontinued from the trial.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

In the initial 104-week trial, all subjects were given a Subject Identification Card identifying them as participants in a research trial. The card contains trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency.

7.1.1.4 Concomitant Medications Review

7.1.1.4.1 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial.

7.1.1.5 Trial Compliance (Medication/Diet/Activity/Other)

As part of the routine recording of the amount of trial treatment taken by each subject, the number of pills remaining in trial packaging will be counted and recorded at each regular visit. These results will be used to calculate subject compliance. Instances where the subject took more or less trial medication than prescribed will be recorded on the study medication eCRF. Events that meet criteria for overdose as defined in Section 7.2.1 will also be reported as an AE (ECI or SAE, as applicable). To monitor for potential misuse, the site will document significant discrepancies in drug returns where the subject or trial partner returns less trial medication than expected but denies taking extra trial medication (e.g., lost or missing medication equivalent to more than one pill per week).

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Trial Partner Attendance at Trial Visits

The trial partner is expected to accompany the subject to all trial visits when feasible. At the discretion of the investigator, exceptions are acceptable, such as visits where no clinical measures are scheduled for administration to the trial partner. However, in these instances, the trial partner should be contacted by phone to complete AE, concomitant medication, and trial medication compliance review. For additional details, the Sponsor may be consulted.

7.1.2.2 Physical Assessments/Examinations

7.1.2.2.1 Vital Signs

The following vital signs will be measured and recorded: pulse (beats/minute), blood pressure (mm Hg), temperature (ºC/ºF), and respiratory rate (breaths per minute). Blood pressure should be measured in the sitting position.

7.1.2.2.2 Body Weight (kg/lbs)

Body weight data will be collected and recorded. Body weight data will be collected without shoes and with heavy clothing removed. Body weight should be performed on the same scale for the same individual. Measurements should be recorded to the nearest kilogram/pounds.

7.1.2.2.3 Directed Physical and Neurological Examinations

A routine physical and neurological examination with focus on subject-specific signs and symptoms should be performed. If the subject is discontinued for any reason during the treatment phase, every attempt should be made to perform a final physical examination.

7.1.2.2.4 Skin Examinations

To monitor for hypopigmentation, skin examinations will be performed by a site physician at the visits specified in Section 6.0, Trial Flow Chart. At Weeks 130, 156, 208, 260, 312, and 364, a site physician will perform a directed examination of the subject's skin. In addition, sites will instruct subjects to perform a self-examination of their skin between clinic visits (with the assistance of their trial partner, if needed). Subjects should report any abnormal loss of skin pigment to the site. The site physician's examination will focus on exposed skin and any areas of pigment loss noted by the subject or trial partner. If a clinically significant area of hypopigmentation is observed, the site should refer the subject to a dermatologist or medical expert for further follow-up. At each scheduled assessment, the following information should be recorded: whether significant sites of skin hypo- or depigmentation were observed, and any adverse events.

Based on the local standard of care, the investigator should refer subjects to a dermatologist or medical expert if: 1) a clinically significant area of skin develops hypopigmentation compared to baseline*; or 2) if needed based on their clinical judgment. The following criteria are provided to guide the investigator but are not meant to be inclusive or to require referral in all cases.

1) A clinically significant area of hypopigmentation may include:
    a) those greater than 3x3 cm
    b) a smaller area (e.g., 1x1 cm) on the face or hands
    c) a speckled pattern involving a larger amount of body surface area or
    d) a smaller area (e.g., 1x1 cm) of complete pigment loss.

Hypopigmentation for criterion 1 is defined as a decrease in skin color relative to the surrounding skin and its prior baseline appearance.

2) Clinical judgment criteria include:

a) In the investigator's judgment, the hypopigmentation requires evaluation by an expert (e.g., small lesions on the face), or

b) The subject or caregiver is distressed by the appearance of the skin lesion or hypo/depigmentation.

Dermatologists will evaluate and treat any lesions based on local standard of care. No special procedures are required per protocol.

*In this trial baseline is considered the skin examination performed by a dermatologist in the initial 104-week trial at screening. For those subjects who did not have a skin examination performed by a dermatologist in the initial 104-week trial at screening, baseline should be considered either the full body skin examination performed by a dermatologist at 6 months, or, if that is unavailable, the directed skin examination performed by the site physician at the EOT visit in the initial 104-week trial.

7.1.2.2.5 12-Lead Electrocardiogram (ECG)

A 12-Lead Electrocardiogram will be performed according to the instructions in a separate ECG Instruction Manual. Note: Triplicate measurements of ECG will be required if there is an observation of QTc prolongation during this trial. Otherwise, single measurements should be done at specified time points indicated in Section 6.0, Trial Flow Chart.

7.1.2.2.6 Structural Magnetic Resonance Imaging (MRI)

Structural MRI for safety monitoring may be conducted at an unscheduled visit if the investigator considers that it is clinically indicated due to an adverse event.

Amyloid-related imaging abnormalities that arise during the trial should be handled as follows:

1) Trial medication should be discontinued if an imaging abnormality consistent with intraparenchymal macrohemorrhage appears or a **clinically symptomatic** incident vasogenic edema, microhemorrhage, or superficial siderosis is seen.

2) If symptomatic cerebral vasogenic edema occurs, MRI scans should be repeated within three to four weeks to assess stability and then performed every four to six weeks (or as clinically indicated) until the vasogenic edema resolves. Treatment with high dose dexamethasone can be considered, as suggested by the US FDA, if associated symptoms are severe.

3) For subjects who present with new clinically symptomatic microhemorrhages or superficial siderosis, an MRI re-scan at three to four weeks should be performed in order to evaluate their stability.

4) Re-dosing can be considered with Sponsor approval based on investigators' clinical judgment if clinical symptoms associated with symptomatic vasogenic edema, microhemorrhage, or superficial siderosis have resolved.

5) For intraparenchymal macrohemorrhage, subjects must be discontinued from study medication and cannot resume dosing.

7.1.2.3 Cognitive and Clinical Assessments

Quality control is an essential part of all clinical trials. For AD trials, it is particularly important to monitor clinical ratings. This trial will include a review by outside expert(s) of the ratings administered as determined by the Sponsor.

Raters of clinical assessments will undergo the applicable training prior to conducting assessments in the trial. Further, rater performance on these assessments will be carefully evaluated and monitored by central external experts to ensure and maintain adequate reliability throughout the trial. Details will be specified in the Manual of Assessments and in training materials provided by the rater training vendor. **In order to qualify for the trial, raters must be approved by the Sponsor, which will require successful completion of a trial specific rater training program.** To ensure the continued quality of the assessments, raters will be asked to audio record certain interviews and ratings through Week 130 (please see the MedAvante Manual for specific details regarding assessments to be audio recorded). Some or all of these recorded interviews will be reviewed by outside experts. Raters may be provided feedback on the quality of their interviews and ratings reviewed by the outside experts via QCAT, e-mail, telephone or in face-to-face meetings in order to develop and maintain good rater reliability. Based on this feedback, raters should consider changing their initially recorded scores if errors are identified. Routine rater meetings may be conducted to assess and maintain reliability for the duration of the trial. Raters who do not perform adequately may be required to undergo additional remediation or may be replaced.

While concerns have been raised that audio recordings could theoretically compromise subjects' privacy, this issue must be balanced with the needs to conduct methodologically adequate and scientifically rigorous trials that are capable of testing the key hypotheses. Given that the key endpoints in this trial involve subjective judgments, monitoring the adequacy of subject interviews and ratings is essential and part of good research methodology. Prior studies have clearly demonstrated that the failure to adequately monitor such ratings can substantially increase the risks of failed trials [12; 13]. Recorded interviews will be secured using state of the art methods to ensure privacy. Recordings will only be reviewed by approved trial personnel for quality control purposes and will be destroyed within two years of the completion of the trial, unless local regulatory authorities or IRBs/ERCs have different requirements for storage.

Subjects may participate in this protocol and also participate in certain observational studies (including studies with neuroimaging), if approved by the Sponsor. These studies must involve only limited cognitive testing.

7.1.2.3.1 Confirmation of Progression to Probable AD Dementia

The principal investigator or qualified designee* will assess whether or not the subject may have progressed to dementia at all visits during the long term trial until the investigator or qualified designee considers the subject as having progressed to dementia. Cases of progression in the long term trial will not be reviewed by an adjudication committee; therefore the final decision on progression will be the opinion of the investigator or qualified designee.

Note: For subjects who were judged to have progressed to AD or non AD dementia by the adjudication committee in the initial 104-week trial, the investigator should document in their study records the reasons they judge that the subject had not progressed to dementia prior to the subject entering the extension trial.

* Note: Please refer to the Manual of Assessments for qualifications required of the Qualified Designee when the Qualified Designee completes the assessment of progression to probable AD dementia.

7.1.2.3.2 Clinical Dementia Rating (CDR)

The CDR [15] will be administered to both the subject and the subject's trial partner/informant in paper form, and the CDR Sum of Boxes (CDR-SB) will be scored and recorded by a qualified, trained rater according to the instructions in the Manual of Assessments. When possible, the CDR should be administered as the first clinical rating during relevant visits. Additional detailed information concerning administration, scoring and documentation may also be provided by the rater training vendor.

7.1.2.3.3 Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog)

The ADAS-Cog13 (including number cancellation and delayed recall) [16] will be administered to the subject in paper form and scored and recorded by a qualified, trained rater according to the instructions in the Manual of Assessments. When possible, the ADAS-Cog should be administered to subjects after the CDR is administered. Additional detailed information concerning administration, scoring and documentation may also be provided by the rater training vendor.

7.1.2.3.4 Controlled Oral Word Association Test (COWAT)

The COWAT is a short, paper/pencil measure of phonemic fluency and executive functioning from the Multilingual Aphasia Examination [17]. The COWAT will be administered to the subject and scored by a qualified, trained rater according to the instructions in the Manual of Assessments. Additional detailed information concerning administration, scoring and documentation may also be provided by the rater training vendor.

7.1.2.3.5 Trail Making Test (A&B)

The Trail Making Test [18; 19], a brief paper/pencil assessment of visual scanning (Part A) and visuomotor sequencing (Part B), will be administered to the subject and scored by a qualified, trained rater according to the instructions in the Manual of Assessments. Additional detailed information concerning administration, scoring and documentation may also be provided by the rater training vendor.

7.1.2.3.6 CERAD Verbal Fluency (CVF)

The CVF Test [20], a brief paper/pencil measure of semantic processing and executive functioning, will be administered to the subject and scored by a qualified, trained rater according to the instructions in the Manual of Assessments. Additional detailed information concerning administration, scoring and documentation may also be provided by the rater training vendor.

7.1.2.3.7 Digit Span Test

Digit Span, a brief paper/pencil measure from the Wechsler Adult Intelligence Scale-III [21], will be administered to the subject and scored by a qualified, trained rater according to the instructions in the Manual of Assessments. Digits Forward assesses attention, while Digits Backward also measures working memory and mental tracking. Additional detailed information concerning administration, scoring and documentation may also be provided by the rater training vendor.

7.1.2.3.8 Digit Symbol-Coding (DSC)

The DSC subtest of the Wechsler Adult Intelligence Scale-III [21] is a brief paper/pencil task assessing attention, psychomotor speed and visuomotor coordination. The DSC will be administered to the subject and scored by a qualified, trained rater according to the instructions in the Manual of Assessments. Additional detailed information concerning administration, scoring and documentation may also be provided by the rater training vendor.

7.1.2.3.9 Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL$_{MCI}$)

The ADCS-ADL$_{MCI}$ [22], a functional assessment adapted for MCI trials, will be administered to the subject's trial partner/informant in paper form and scored and recorded by a qualified, trained rater according to the instructions in the Manual of Assessments. Additional detailed information concerning administration, scoring and documentation may also be provided by the rater training vendor.

7.1.2.3.10 Mini-Mental State Examination (MMSE)

The paper version of the MMSE [23], a brief measure of cognition, will be administered to the subject and scored and recorded by a qualified, trained rater according to the instructions

in the Manual of Assessments. Additional detailed information concerning administration, scoring and documentation may also be provided by the rater training vendor.

7.1.2.3.11 Columbia Suicide Severity Rating Scale (C-SSRS)

Suicidal ideation and behavior will be prospectively assessed using the C-SSRS [24]. The paper version of the C-SSRS should be administered by trained raters at specified time points, as indicated in the Trial Flow Chart, as well as at unscheduled visits as clinically indicated. Site staff should review the contents of the C-SSRS for completeness and then transcribe the data to the eCRF.

Subjects who at any time during this study report an AE of suicidal ideation or behavior, either between visits or during visit interviews, must be assessed by the investigator or qualified designee. Subjects who report suicidal ideation with intent, with or without a plan or method (i.e., a positive response to items 4 or 5 in the assessment of suicidal ideation on the C-SSRS) or suicidal behavior must be evaluated that day by a psychiatrist or other trained mental health professional who is a licensed psychologist, social worker or nurse practitioner (or comparable professional qualification in countries outside the United States). Only subjects whose suicidal ideation is passive, who expressly deny any intent to act, and who, after evaluation, are not judged to be at serious risk for self-harm during the course of the trial may continue with trial treatment; others must be discontinued from trial treatment and receive appropriate clinical follow-up care to assure their safety. After appropriate follow-up care, if the investigator judges that the subject can safely resume trial treatment, re-dosing can be considered with Sponsor approval.

All reports of suicidal ideation or behavior must be recorded as an Event of Clinical Interest (ECI) (See Section 7.2.3.2). Sites are to indicate which health care professionals are to be responsible for acute care on-site and to specify referral center(s) to be used for further evaluation.

The C-SSRS (Since Last Visit paper versions) will be administered to the subject and scored by a qualified trained rater as described in the Manual of Assessments. Additional detailed information concerning administration, scoring, and documentation may also be provided by the rater training vendor.

7.1.2.3.12 Neuropsychiatric Inventory (NPI)

The NPI [25] is an interview-based tool for assessing behavioral domains common in dementia (Hallucinations, Delusions, Agitation/aggression, Dysphoria/depression, Anxiety, Irritability, Disinhibition, Euphoria, Apathy, Aberrant motor behavior, Sleep and night-time behavior change, Appetite and eating change) in terms of frequency, severity and distress; it is widely used in clinical trials to assess behavior in AD and other dementias. The NPI (paper version) will be administered to the subject's trial partner/informant and scored by a qualified, trained rater according to the instructions in the Manual of Assessments. Additional detailed information concerning administration, scoring and documentation may also be provided by the rater training vendor.

7.1.2.3.13 Modified Resource Utilization in Dementia (RUD) Lite Questionnaire

A modified RUD Lite Questionnaire will be administered to the subject's trial partner/informant in paper form and documented by a qualified, trained rater according to the instructions in the Manual of Assessments.

7.1.2.3.14 Health Economic Assessment (HEA)

The HEA will be administered to the subject's trial partner/informant in paper form and documented by a qualified, trained rater according to the instructions in the Manual of Assessments.

7.1.2.3.15 EuroQol Five Dimension Questionnaire (EQ-5D)

The EQ-5D will be completed by the subject's trial partner/informant in paper form and reviewed by a qualified, trained rater according to the instructions in the Manual of Assessments.

7.1.2.3.16 Confusion Assessment Method (CAM)

The CAM is completed by the rater based on information provided by other sources (i.e. medical records, asking the subject questions). It should be completed only if and when an adverse event of delirium is suspected to ascertain the diagnosis of delirium.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in Section 12.2.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 4.

Table 4 Laboratory Tests

Hematology	Chemistry	Urinalysis
Basophils	Albumin	Blood
Eosinophils	Alkaline phosphatase	Glucose
Hematocrit	Alanine aminotransferase (ALT)	Ketones
Hemoglobin	Aspartate aminotransferase (AST)	Microscopic exam, if abnormal results are noted
Lymphocytes	Bicarbonate	pH
Monocytes	Blood Urea Nitrogen (BUN)	Protein
Neutrophils	Calcium	Specific gravity
Platelets	Chloride	
RBC	Cholesterol	
WBC	Creatinine	
	Glucose	
	Phosphorus	
	LDH	
	Potassium	
	Sodium	
	Total Bilirubin	
	Total protein	

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who permanently discontinue from treatment will be discontinued from the trial.

7.1.4.2 Blinding/Unblinding

TRIAL TREATMENT IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE SUBJECT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND THE SUBJECT UNLESS NECESSARY.

For emergency situations where the investigator or sub-investigator needs to identify the drug used by a subject and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or sub-investigator the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the sponsor. The emergency unblinding call-center will make a record promptly however, the investigator or sub-investigator must enter the intensity of the adverse experiences observed, their relation to study drug, the reason thereof, etc., in the medical chart etc., before unblinding is performed.

Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this trial, IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the subject.

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event. Progression of the condition under study (prodromal AD) is not considered an adverse event unless it is assessed as drug-related by the investigator, or is characterized by unusual or atypical decline for AD progression in the judgment of the investigator, or meets criteria for a serious adverse event (see Section 7.2.3.1).

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be

excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 14 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

In this trial, an overdose is any dose higher than two times the daily dose of trial medication in a calendar day specified in Section 5.2.2.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 14 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion,

missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a cancer;
- Is associated with an overdose.

Refer to Table 5 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the

investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder.

3. Certain adverse events associated with potential for abuse (euphoric mood, mania, hypomania, or similar events); additional information may be requested for other adverse events associated with potential for abuse, but these AEs will not be considered ECIs;

4. ALT or AST ≥3 x ULN and a ≥20% increase from baseline;

5. **Incident vasogenic edema in post-treatment brain MRI scans;

6. **Incident intraparenchymal macrohemorrhage in post-treatment brain MRI scans;

7. **Incident superficial siderosis in post-treatment brain MRI scans;

8. **Incident microhemorrhage in post-treatment brain MRI scans;

9. Suicidal ideation and/or suicidal behavior;

10. Delirium that is ascertained by the investigator or a qualified designee. The Confusion Assessment Method (CAM) [26] should be used to verify delirium whenever feasible;

11. A clinically significant rash in the investigator's judgment (such as a duration >2 weeks OR a rash that is >10% BSA, OR a rash causes significant discomfort not relieved by topical medication) OR a severe rash (as defined in Section 5.6);

12. Adverse events of clinically significant skin hypo- or depigmentation (see Section 7.1.2.2.4 for details);

    A separate guidance document will be provided to sites for follow-up care of elevated LFT. Follow-up care for clinically significant rashes and severe rashes will also be detailed in another guidance document to sites, which includes evaluation by a dermatologist, photographs of skin lesions, and biopsy if indicated. For severe rashes, an adjudication committee will be adjudicating all cases of Stevens-Johnson Syndrome, erythroderma, toxic epidermal necrolysis, or DRESS syndrome based on photographs, biopsy results, and other available clinical data. Details will be described in the adjudication committee charter.

    **Since routine MRI monitoring for safety has been discontinued, the central Reading Center is not automatically performing central reading for safety. Therefore, during the main study and the extension, the site investigator or radiologist should perform a local reading, as necessary. In some cases, central reads for safety may be performed. In the event that an Amyloid Related Imaging Abnormality (ARIA) is detected, then the Sponsor may request that the MRI be submitted for central reading.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 5. The investigator's assessment of causality is required for each adverse event. Refer to Table 5 for instructions in evaluating adverse events.

Table 5 Evaluating Adverse Events

Maximum Intensity	**Mild**	awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)
	Moderate	discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)
	Severe	incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)
Seriousness	A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect (**in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is associated with an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this trial? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE AND APPROPRIATE RECONSENT OBTAINED. WHERE RESTRICTED LOCALLY BY IRS (INCLUDING SITES IN FRANCE): FOR SAEs JUDGED TO BE RELATED TO TRIAL DRUG, SUBJECTS MUST BE DISCONTINUED FROM TRIAL DRUG.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Executive Oversight Committee

The Executive Oversight Committee (EOC) comprises members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the external Data Monitoring Committee (eDMC) regarding the trial.

7.3.2 Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (DMC) will monitor the safety data from this trial at the appropriate frequency and for the duration required per the DMC charter. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the trial in any other way (e.g., they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

The DMC will make recommendations to the EOC regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.2.13 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding composition, responsibilities and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DMC. The DMC will monitor the trial at an appropriate frequency, as described in the detailed DMC charter. The DMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

7.3.3 Clinical Adjudication Committee

A Clinical Adjudication Committee (CAC) will evaluate the following events for the purposes of confirming them according to the criteria in Section 8.0 – Statistical Analysis Plan, as well as evaluating the presence of confounding factors.

- For severe rashes, an external clinical adjudication committee will adjudicate all cases of Stevens-Johnson Syndrome, erythroderma, toxic epidermal necrolysis, or DRESS syndrome based on photographs, biopsy results, and other available clinical data.

All personnel involved in the adjudication process will remain blinded to treatment allocation throughout the trial. Specific details regarding endpoint definitions can be found in the Adjudication Charter.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 8.2).

8.1.1 Efficacy Analyses

The primary and key secondary endpoints, primary analysis population, and statistical methods that will be employed for the efficacy analyses are presented in Table 6.

There are no formal hypotheses for this trial. All efficacy measurements analyzed during the initial 104-week trial will continue to be collected and analyzed in the long term trial. The primary endpoint is the 30-Month (6 months after the primary timepoint from the initial 104-week trial) change-from-baseline treatment difference on CDR-SB.

8.1.2 Safety Analyses

The All-Subjects-as-Treated population will be employed for safety analyses. The prespecified events of interest (Tier-1 events) are 1) Microhemorrhage, superficial siderosis or macrohemorrhage; 2) vasogenic edema; 3) delirium; and 4) rash ECI. P-values and 95% confidence intervals for between-treatment differences in the percentage of subjects with events will be calculated using the Miettinen and Nurminen method [27].

8.1.3 Power and Sample Size

There are no sample size calculations for the long term trial, as there are no formal hypotheses. Subjects who complete the initial 104-week trial will be eligible for the long term trial. The number of individuals enrolled in the extension will not exceed the number enrolled in the base study.

8.1.4 Interim Analyses

The independent eDMC will routinely evaluate unblinded safety analyses of all trial subjects while the initial 104-week trial is blinded and as described in their charter. Additional safety analyses may be conducted throughout the trial as requested by the eDMC. The sponsor will be unblinded after completion of the initial 104-week trial.

8.2 Statistical Analysis Plan

8.2.1 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR.

The sponsor will be unblinded after completion of the initial 104-week trial. But prior to that, the extension trial will be conducted as a double-blind study under in-house blinding procedures. Planned interim analyses are described in Section 8.2.13. Blinding to treatment assignment will be maintained at all investigational sites. The results of interim analyses will not be shared with the investigators prior to unblinding of the trial. Subject-level unblinding will be restricted to an external unblinded group of statisticians.

Treatment-level results of the interim analysis will be provided by the external statisticians to the eDMC (and any necessary consultants thereto, e.g., ophthalmologists). Limited additional SPONSOR personnel may be unblinded to the treatment level results of the interim analysis (analyses), if required, in order to act on the recommendations of the eDMC. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the external statisticians.

Prior to final study unblinding, the external statisticians will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol violators, or data validation efforts.

8.2.2 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0.

8.2.3 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below.

8.2.3.1 Efficacy Endpoints

It is noted that baseline refers to the baseline from the initial 104-week trial.

8.2.3.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from Baseline in the CDR-SB score at Week 130.

8.2.3.1.2 Exploratory Efficacy Endpoints

Exploratory endpoints include

- the time to progression to probable AD dementia as determined by investigator-diagnosis; and the following at all scheduled timepoints:
- the change from Baseline score in the CDR-SB (with the exception of Week 130 which is designated as the primary endpoint);
- the change from Baseline score in the CCS-3D;
- the change from Baseline score for the composite cognition subscale (memory, orientation, judgment and problem solving) and composite functional subscale (home and hobbies, personal care and community affairs) of the CDR;
- the change from Baseline score for: ADCS-ADL$_{MCI}$, ADAS-Cog13, Number Cancellation, MMSE, CCS-2D, and NPI;
- Modified RUD Lite, HEA, and EQ-5D;
- the change from Baseline score for the three domain z-scores of the CCS-3D (episodic memory, executive function, and attention/processing speed);
- the change from Baseline score for the domain-specific individual components of the CCS-3D: Immediate Word Recall (ADAS-Cog), Delayed Word Recall (ADAS-Cog), Word Recognition (ADAS-Cog), and Orientation (ADAS-Cog), Digit Span Test (Forwards), DSC, Digit Span Test (Backwards), Trails A Test, Trails B Test, COWAT, and CERAD Verbal Fluency Test.

8.2.3.2 Safety Endpoints

Refer to Section 8.2.8 for initial description of safety measures. It is noted that baseline refers to the baseline from the initial 104-week trial.

8.2.3.3 Derivations of Efficacy Endpoints

For the handling of missing data within an endpoint (i.e., if an individual subquestion needed for a total score is missing) see Section 8.2.7.5

The CCS-3D will be calculated as the mean of three domain z-scores (episodic memory, executive function, and attention processing). In a similar fashion, each of these three domain z-scores will be calculated as the mean of domain specific tests (after transformation to z-scores), as follows:

> Episodic Memory: Immediate Word Recall, Delayed Word Recall, Word Recognition, and Orientation (all from ADAS-Cog);
>
> Executive Function: Digit Span Test (Backwards), Trails B Test, COWAT, CERAD Verbal Fluency Test;
>
> Attention/Processing Speed: Trails A Test, Digit Span Test (Forwards), DSC

The z-scores [(observed value - baseline mean)/ baseline standard deviation)] for each of the individual component tests will be calculated at each timepoint using the baseline mean and standard deviation of all treated subjects. Prior to taking the average of three domain scores for the computation of CCS-3D, each of the three domain scores will be normalized in a similar fashion.

The CCS-2D endpoint will be constructed by averaging the z-scores from five component tests: Immediate Word Recall (ADAS-Cog), Word Recognition (ADAS-Cog), Orientation (ADAS-Cog), COWAT, and CERAD Verbal Fluency.

8.2.4 Analysis Populations

8.2.4.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population for a given endpoint consists of all randomized subjects who:

- receive at least one dose of study treatment,
- have both 1) a baseline measurement for the analysis endpoint and 2) at least one within-analysis-window (± 6 weeks) post-dose, post-randomization observation for the analysis endpoint, and
- are PET positive.

All available observations from the initial 104-week trial will be included in the relevant model-based FAS analyses. Observations from the long term trial will be included according to the principles outlined above, with the following additional requirement: the subject must have taken at least one dose of study medication within the 28 days preceding the 104-week visit and within the 28 days following the 104-week visit.

The Modified Full Analysis Set (MFAS) population will be utilized for sensitivity analyses and is defined identically to the FAS population with one exception: patients will only be required to have either 1) a baseline measurement for the analysis endpoint or 2) at least one within-analysis-window (± 6 weeks) post-dose, post-randomization observation for the analysis endpoint, but not necessarily both.

The MFAS population will be utilized to conduct sensitivity analyses in this study for the primary endpoint (CDR-SB 30-Month CFB).

Though no Per-Protocol analyses are planned, a list of protocol violations/violators will be maintained. The final determination on protocol violations will be made prior to the final unblinding of the database and will be documented in a separate memo.

Subjects will be included in the treatment group to which they are randomized for the analysis of efficacy data using the FAS population.

8.2.5 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least one dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.2.6 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 8.2.8. The final analysis is expected to be carried out using SAS v9.3.

8.2.7 Statistical Methods for Efficacy Analyses

8.2.7.1 Primary Efficacy Analysis

The primary efficacy endpoint is the change from Baseline (CFB) in CDR-SB score at Week 130. Basic summary statistics (means and standard deviations, as observed), will be calculated.

A delayed start design will be used to support the potential disease modifying effect of MK-8931 by comparing the 40 mg/40 mg arm to the Pbo/40 mg arm. However, due to increased variance and anticipated dropout rate over time, the study is not powered to demonstrate significance on these endpoints, even if significance was demonstrated at 24 months in the initial study.

The 12 mg/12 mg arm will be compared to the Pbo/40 mg arm in a similar fashion.

All available data from the initial 104-week trial will be utilized in the analyses, even that from subjects who do not continue into long term trial. It is possible that the 40 mg dose may be dropped for reasons due to safety, in which case all subjects would receive 12 mg. The primary comparison in this case would be between the 12 mg / 12 mg arm and the Pbo / 12 mg arm (with any subjects receiving 40 mg excluded from the analysis).

A longitudinal ANCOVA model will be used on the change scores, with time treated as a categorical variable so as not to impose any restriction on the trajectory of the means over time. The analysis model includes treatment, time, the time-by-treatment interaction, APOE4 genotype (APOE4 positive, APOE4 negative), gender, geographic region, and the use of acetylcholinesterase inhibitors at screening (Use, Do Not Use) as categorical terms, with age and baseline MMSE score as continuous covariates. The baseline value of the dependent

variable, as well as the baseline-by-time interaction term will also be included. Model-based estimates of the mean change scores and the mean treatment difference on the change scores will be provided, along with the corresponding confidence intervals and p-values for the mean treatment differences. An unstructured covariance matrix will be used to model the correlation among repeated measurements.

Three supportive analyses will be conducted on the primary efficacy endpoint. These analyses will be conducted to assess the effect of 1) missing data using a pattern-mixture model "tipping-point" approach, which is intended to provide a measure of robustness in the (unobservable) event that a larger-than-expected proportion of the missing data be missing-not-at-random (MNAR) 2) the use of off-regimen data after the subject has permanently discontinued trial medication or after the subject has initiated AChEIs and 3) analysis using the cLDA model on the MFAS population.

For the first sensitivity analyses (tipping-point), the model-based estimates of the mean treatment difference on the change scores, along with the corresponding confidence intervals and p-values will be provided for a range of *c* values which have been subtracted from the values imputed for the active arms (see Section 8.2.7.5 for more details). Of specific interest is the smallest *c* value that, for a given endpoint, transforms a "statistically significant" result to a "non-statistically significant" result (per the pre-defined α-level used in the initial 104-week trial).

For the second sensitivity analysis (excluding observations obtained after study medication discontinuation or after the initiation of AChEIs), the model-based estimates of the mean treatment difference on the change scores, along with the corresponding confidence intervals and p-values will be provided.

For the third sensitivity analysis (cLDA model on the MFAS population), the analysis of the primary efficacy endpoint will be conducted using a constrained longitudinal data analysis (cLDA) method proposed by Liang and Zeger [28]. This model assumes a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. The response vector consists of baseline and the values observed at each post-baseline time point. The model-based estimates of the mean treatment difference on the change scores, along with the corresponding confidence intervals and p-values will be provided as obtained using the cLDA model, with all of the same covariates that were included in the primary model (now excluding the terms for baseline and baseline-by-time interaction). An unstructured covariance model will be used.

Table 6 Analysis Strategy for Primary Endpoints

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint				
CFB in CDR-SB scores at 130 Weeks	P	Longitudinal ANCOVA	FAS	Model-based
	S	Longitudinal ANCOVA	FAS	Pattern-Mixture Model (Tipping Point)
	S	Longitudinal ANCOVA (Exclude data collected after the introduction of AChEIs and/or study medication discontinuation)	FAS	Model-based
	S	cLDA	MFAS	Model-Based
AChEIs= acetylcholinesterase Inhibitors; CFB=Change from baseline.				

8.2.7.2 Exploratory Efficacy Analyses

One exploratory endpoint is the time to progression to probable AD dementia as determined by investigator-diagnosis (noting that the formal adjudication process utilized in the initial 104-week study, will not be utilized in the long-term safety study). All available data from the initial 104-week trial will be utilized in the analysis. A Cox proportional hazard model adjusting for APOE4 genotype (APOE4 positive, APOE4 negative), gender, geographic region, and the use of acetylcholinesterase inhibitors at screening (Use, Do Not Use) as categorical terms, with age and baseline MMSE score as continuous covariates will be used to compare the hazard functions of the 40 mg/40 mg arm to the Pbo/40 mg arm, as well as to compute the hazard ratios and the corresponding confidence intervals (CIs). Subjects who reach the maximum treatment duration will be considered as completers and will be censored at that timepoint.

The 12 mg/12 mg arm will be compared to the Pbo/40 mg arm in a similar fashion.

If the analysis model fails to converge due to the presence of too many factors in the model (i.e., empty cells), then factors will be removed one at a time until the model does converge. Factors will be removed in the following order: geographic region, gender, use of acetylcholinesterase inhibitors at screening, and APOE4 genotype.

For all other continuous exploratory endpoints, the same model that is used for the primary endpoint will be used as were specified in Section 8.2.3.1.

No sensitivity analyses will be conducted on any of the exploratory endpoints.

8.2.7.3 Health Economic Endpoints

The Modified RUD Lite will be evaluated by tabulating the counts and percentages of each living-arrangement category across the treatment arms and visits.

For HEA, the counts and percentages of each category of non-trial medical visit will be tabulated by treatment group and visit.

The EuroQoL Five Dimension Questionnaire (EQ-5D) will be evaluated by tabulating the counts and percentages of each health dimension by treatment group and visit. Basic summary statistics will also be computed for the assessment of subject health state (0-100 scale) by treatment and visit.

8.2.7.4 Pharmacogenetic Analyses

The relationship between APOE genotype and the following clinical outcomes: CDR-SB, ADAS-Cog and ADCS-ADL_{MCI} will be evaluated as an exploratory analysis.

Additional exploratory pharmacogenetics (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or for certain adverse events. Genomic markers of disease may also be investigated. Pharmacogenetic studies may use PK/PD results or clinical outcomes. Any nominally significant PGt relationships to outcome will require validation in future clinical trials.

8.2.7.5 Accounting for Missing Data

It is expected that Missing at Random and Missing Completely at Random (MAR/MCAR) mechanisms will underlie most of the missingness. Reasons for discontinuation from the study may include lack of efficacy, adverse experiences, relocation, withdrawal of consent, protocol violations, and/or data processing issues. Missing data caused by relocation and data processing issues are likely to be MCAR. On the other hand, missing data caused by discontinuation due to lack of efficacy may belong to MAR because the discontinuation may depend on the observed efficacy outcomes. The MAR or MNAR mechanisms might each underlie the other reasons to some extent. If treatment in large part determines the loss of data for these other reasons (such as clinical or laboratory adverse experiences), the mechanism may be close to MAR because treatment assignment is an observed variable and included in the analysis model. Based on results from similarly-designed, previously-conducted trials, missing data due to other reasons is relatively infrequent. Of note, in the event that there are no missing data, the estimated treatment difference from the above cLDA model will be identical to that from a traditional longitudinal ANCOVA model which uses the baseline value as a covariate.

A pattern-mixture model based on the tipping-point approach will be used to assess the robustness of the primary analysis approach. For a given constant, *c*, the tipping point analysis is conducted in a fashion similar to that used in standard multiple imputation [29; 30; 31], whereby *m* complete datasets are randomly generated using the original observed dataset. These *m* complete datasets are subsequently analyzed using the primary model, and the results of those analyses are then combined. The construction and analysis of these *m* (=50) datasets requires four primary steps:

a. Using a Markov Chain Monte Carlo method [32], make the observed dataset monotone-missing. This will be accomplished for each treatment group using "PROC MI" within SAS 9.3 by utilizing the options "mcmc chain=multiple impute=monotone;", in conjunction with all of the covariates (excluding treatment) included in the primary analysis model. The random seed will be set equal to 8931019. This step will generate *m* monotone-missing datasets.

b. Applying parametric regression to the monotone-missing datasets, impute the missing values in a stepwise fashion starting with the first postdose timepoint. This will be accomplished for each treatment group using "PROC MI" within SAS 9.3 utilizing the option "monotone reg", in conjunction with all of the covariates (excluding treatment) included in the primary analysis model. The random seed will be set equal to 8931019. This step will generate *m* complete datasets.

c. To implement the tipping-point aspect of the procedure, subtract a constant *c* from each of the imputed values of the active arms (to the detriment of active).

d. Analyze each of the post-imputation complete datasets using the primary model, obtaining point estimates for the mean of interest (e.g., change-from-baseline treatment difference at 104 weeks) and the associated variance.

Using "proc mianalyze" within SAS 9.3, the m=50 means and variances from the m analyses will be combined to obtain the final test statistic and p-value [29]. The final test statistic $\bar{Q} / (T^{(1/2)})$ is approximately distributed as t_v, where $\bar{Q}$ is the sample mean of the m mean estimates, $T=\bar{U} + (m+1)(B/m)$, $\bar{U}$ is the sample mean of the m variance estimates, and B is the sample variance of the m mean estimates. The degrees of freedom, ν, will be computed as follows [33], $\nu = [(\nu_1)^{-1} + (\nu_2)^{-1}]^{-1}$, where $\nu_1 = (m-1)[1 + (\bar{U}/(1+m^{-1})B)]^2$ and $\nu_2 = (1-\gamma)\nu_0(\nu_0+1) / (\nu_0+3)$, with $\gamma = (1+m^{-1})B / T$ and where ν_0 represents the complete-data degrees of freedom.

This procedure will be repeated (using the same *m* imputed datasets) until the smallest *c* is found such that the "significant" result turns "non-significant" (i.e., $p \geq 0.02495$). This tipping point value *c* provides a measure of robustness of the primary result. A relatively large value of *c* implies better robustness of the primary analysis against the impact of missing data in the study. It is noted that when *c*=0 the tipping point analysis described above corresponds to an analysis conducted under the assumption that the missing data are MAR. For values of *c* larger than 0, the tipping point analyses do not assume that the missing values follow a MAR mechanism. In fact, the analysis is based on a special MNAR mechanism in which all missing data in the active arm are assumed to have a worse response

by a constant amount of *c* than the values would have had under MAR, while the missing data in the control group are assumed to be the same as that obtained under MAR.

It may be necessary to adjust *c*, in order to calibrate between the two analysis approaches (ANCOVA vs. MI), should a value of c=0 yield a different p-value than is produced from the primary ANCOVA analysis model. This will be accomplished by subtracting the calibration value c_{prim} from *c*, where c_{prim} is the offset to be applied to the active arm, per the above MI approach, that will yield the same p-value as produced by the primary ANCOVA analysis.

8.2.7.6 Handling of Missing Items Within a Clinical Assessment

The final scores of the ADAS-Cog, ADCS-ADL$_{MCI}$, NPI, MMSE, CDR-SB, CCS-2D, and CCS-3D are all constructed from multiple subquestions/tests within each assessment. It is possible that one or more subquestions/tests may be missing within each overall assessment. In this event, the last recorded score for this subquestion(s) will be carried forward from the most recent postdose visit. (Last Observation Carried Forward approach). In a similar fashion, missing baseline values will be carried over from the most recent screening visit, if available. Baseline/screening values will never be carried forward to impute missing postdose values. Due to the degenerative properties of AD, with subjects expected to worsen over time, an individual subquestion will not be carried forward for more than one visit. If the same subquestion is missing two visits in a row, then LOCF will be applied to the first missing visit and the subquestion will remain as missing for the second visit (with the total score to then be computed as missing). Further, the total score will be computed as missing if too many subquestions, prior to applying the LOCF approach, are missing (see endpoint-specific details below). This single imputation approach allows the total score to be calculated using the strength of the other subquestions collected at that time, for that subject. The Sponsor believes this approach to be more accurate than either setting the entire score to missing or to imputing the worst possible score. More complicated missing data approaches are not thought to be warranted, since the amount of missing data within an assessment is expected to be extremely low.

For Baseline ADCS-ADL$_{MCI}$ only (from the initial 104-week trial): Past experience indicates that some subquestions on the ADCS-ADL$_{MCI}$ may mistakenly be omitted at the time of administration. Should this occur at baseline, there will be no opportunity to employ the stated LOCF approach. To avoid a missing total score on the ADCS-ADL$_{MCI}$ (and the subsequent removal of the subject from the primary ADCS-ADL$_{MCI}$ population), the worst possible score for that subquestion will be imputed. Note that this imputation approach will only be implemented for ADCS-ADL$_{MCI}$ (given the relatively small impact of the individual subquestions on the overall score) and only at baseline. A total score will only be computed if the number of missing subtotals is strictly less than three.

Endpoint specific details are as follows:

ADAS-Cog and MMSE: The site will be instructed to enter the worst possible score if the subject is unwilling or unable to answer a subquestion due to reasons related to the area the subquestion is trying to address. If the subject is unable to answer a subquestion for some

other reason, then the site will be instructed to leave the subquestion as missing. For both the ADAS-Cog and the MMSE, a total score will be calculated if the original number (prior to applying LOCF) of missing subtotals is strictly less than three.

CCS-3D: If no more than one test is missing within a domain(s), LOCF will be applied to that individual test. Values will not be carried forward for more than one visit. If more than one test is missing within a domain (prior to applying LOCF), then the overall z-score for that domain will be computed as missing. The overall CCS-3D will be computed as missing if any domain score is missing. Note that, in general and unless otherwise noted, the application of LOCF to these individual tests is solely for the computation of the domain z-scores and ultimately the CCS-3D. LOCF will not be applied to these individual tests for the analyses of the individual tests themselves (e.g., LOCF may be applied to the Delayed Word Recall test for the computation of the Episodic Memory domain z-score and ultimately the CCS-3D, but would not be applied for the purposes of analyzing the Delayed Word Recall component individually).

CCS-2D: If no more than one of the five component tests is missing, then LOCF will be applied to that individual test, solely for the purposes of computing the total score. If more than one of the component tests is missing, then the total score will be computed as missing.

CDR-SB, ADCS-ADL$_{MCI}$, and NPI: The CDR-SB, ADCS-ADL$_{MCI}$, and NPI are all administered to the trial partner, not the subject, so no within-assessment missing data are expected (though missing subquestion data is still possible due to data entry error or errors in test administration). For ADCS-ADL$_{MCI}$ and NPI, a total score will be calculated if the original number of missing subtotals is strictly less than three. For CDR-SB, a total score will be calculated if the original number of missing subtotals is strictly less than two.

8.2.8 Statistical Methods for Safety Analyses

Subjects from all three arms (40 mg / 40 mg, 12 mg / 12 mg, Pbo / 40 mg) will be included in the safety analyses. Where applicable, treatment comparisons will be conducted between the 40 mg / 40 mg and Pbo / 40 mg arms, as well as between the 12 mg / 12 mg and Pbo / 40 mg arms.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, vital signs, and ECG measurements. The primary approach for all safety analyses will be an On Drug approach, i.e., one that includes only those observations obtained from the first dose through 14 days after the last dose of study medication. A supportive approach will include all post-treatment observations, including those observations obtained more than 14 days after the last dose of study medication.

The analysis of safety results will follow a tiered approach (Table 7). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be

considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory, vital signs, and ECG parameters (see Section 12.3) that are not pre-specified as Tier-1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 1% of the subjects in any treatment group exhibit the event; all other adverse experiences and predefined limits of change will belong to Tier 3.

The threshold of "at least 1%" was chosen because the expected number of subjects in the ASaT population is expected to be greater than 400 per treatment group. Thus an incidence of at least 1% in a treatment group translates to at least four subjects experiencing that event in the treatment group, which is the minimum number needed to attain statistical significance at α=0.05. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AEs and PDLCs.

Continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters that are not pre-specified as Tier-1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

For this protocol, 1) microhemorrhage, superficial siderosis or macrohemorrhage; 2) vasogenic edema; 3) delirium; and 4) rash ECI (see Section 7.2.3.2 for definition) are considered as Tier 1 events. The broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, a drug related AE, a serious AE, an AE which is both drug-related and serious, and who discontinued due to an AE will be considered Tier 2 endpoints. A composite endpoint of hypopigmentation adverse events is defined based on the following preferred AE terms or equivalent: (noting that MedDRA terms are subject to change over time): skin hypopigmentation, skin depigmentation, vitiligo, leukoderma, hypopigmentation of eyelid, and idiopathic guttate hypomelanosis. This composite AE of hypopigmentation will be considered as either a Tier 2 or Tier 3 AE, per the criteria for Tier 2 AEs defined above. P-values (Tier 1 only) and 95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the Miettinen and Nurminen method [27], an unconditional, asymptotic method.

The prespecified categories of suicidal ideation and behavior will be analyzed per the tiered analysis strategy outlined above, and will be considered as either Tier 2 or Tier 3 AEs, depending on the percent of events observed within each treatment group. Counts for each category will be based upon events observed during the assessment period (without consideration of prior history).

Safety analyses will only be based on subjects who treated in the long term trial. Unless otherwise noted, postdose data from the initial 104-week trial will not be analyzed with data from the long term trial.

Table 7 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint†	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Incident Microhemorrhage, superficial siderosis or macrohemorrhage in brain MRI scans	X	X	X
	Incident Vasogenic edema	X	X	X
	Delirium	X	X	X
	Rash ECI	X	X	X
Tier 2	Any AE		X	X
	Any Serious AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Discontinuation due to AE		X	X
	Specific AEs, SOCs, or PDLCs‡ (incidence ≥1% of subjects in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs or PDLCs‡ (incidence <1% of subjects in all of the treatment groups)			X
	Change from Baseline Results (Labs, ECGs, Vital Signs)			X

†Adverse Experience references refer to both Clinical and Laboratory AEs.
‡Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier-2 endpoints.
Note: SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.

8.2.9 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.2.9.1 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

8.2.10 Multiplicity

In the initial 104-week trial, strong Type I error control is achieved through the utilization of a Bonferroni approach in conjunction with a closed testing sequential approach. Specifically, a separate hypothesis family is created for each of the two active doses, with each hypothesis within a family tested sequentially at the α=0.02495 level.

As there are no formal hypotheses for the long term trial, there is no need for a formal multiplicity strategy. However, 97.51% CIs will be produced for all endpoints with corresponding hypotheses conducted under strong control from the initial 104-week trial, even though formal hypotheses are not defined in this long-term safety trial, and it is acknowledged that strong control is not present.

8.2.11 Sample Size and Power Calculations

8.2.11.1 Sample Size and Power for Efficacy Analyses

8.2.11.1.1 Parameter Estimates

Parameter estimates for the primary endpoint were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Extrapolations out to 30 months (Week 130) were performed on the 24-month (Week 104) parameter assumptions used in the initial 104-week trial and these extrapolations are presented below in Table 8.

Table 8 Parameter Assumptions for CDR-SB

Endpoint	Baseline SD	30m SD	30m CFB Mean (130-Week Placebo/ MK-8931 40 mg Progression Rate)	Corr(Base, 30m)
CDR-SB	0.86	3.05	2.13	0.359
Based on N=151 subjects from ADNI, Late MCIs with either CSF+ (tau/ab142 >= 0.39) or PET+ (pib >1.6), and MMSE>=24.				

8.2.11.1.2 Power Calculations

Power calculations for the change-from-baseline treatment difference at 30 months (Week 130) were performed (via simulation) for CDR-SB even though there are no formal hypotheses for the endpoint in the long term trial. As shown in Table 9 the hypothesis is underpowered at Week 130, both marginally and when applying an informal sequential testing approach. Specifically, it is possible that formal statistical significance may be observed in the initial 104 week trial (under the prespecified multiplicity approach), while nominal marginal significance (ie, p-value < 0.02495) fails to be observed at Week 130, even if the true underlying effect of MK-8931 continues to increase. This is due to the assumed increased variance and dropout rate over time, with 90% of subjects who complete the base study assumed to continue on into the extension.

Table 9 Power Calculations (MK-8931 40 mg / MK-8931 40 mg vs. Placebo / MK-8931 40 mg)

Marginal Probability[†]	**(%)**
CDR-SB at Week 130	73.9
Sequential Probability	
Success[‡] for CDR-SB at Week 104 and CDR-SB at Week 130	73.4
Conditional Probability	
Success[‡] for **CDR-SB** at Week 130 given success on CDR-SB at Week 104	76.1

[†] Marginal power calculations at Week 130 do not require success at Week 104.
[‡] 40 mg dose only
Calculations are based on N=1350 randomized (450 subjects/arm) incorporating the assumed dropout rate of 25% at Week 104 and 37% at Week 130 ($\alpha = 0.02495$).

8.2.12 Subgroup Analyses and Effect of Baseline Factors

Subgroup analyses will be conducted on CDR-SB, CCS-3D, ADCS-ADL_{MCI} at Week 130. The consistency of treatment effect across various subgroups will be assessed through the computation of within group summary statistics (model-based and as-observed), along with nominal 95% CIs. Further, model-based between-group treatment differences (or hazard ratios, as appropriate) and the corresponding 95% CIs will be constructed for those comparisons (active/active vs. placebo/active), for which both treatment groups within the subgroup level have at least 75 subjects (roughly 15% of subjects randomized). No formal statistical testing of the treatment by subgroup interactions will be performed. The following subgroups will be examined:

- Gender (Male, Female);
- Age (< 65, ≥ 65 years of age);
- Race (white, black, Asian, other);
- Ethnicity (Hispanic, Not Hispanic);

- Geographic Region (US/Canada, Europe/Australia/New Zealand, Japan, Rest of World);
- APOE Genotype (APOE 4 positive, APOE 4 negative);
- Disease Severity via MMSE at Screening (24-26, 27-30)
- PET/CSF status at Screening (PET+/CSF+, PET+/CSF-, PET+/CSF Unknown, PET-/CSF+)
- CSF evaluation at Screening (CSF evaluated, CSF not evaluated)
- AD Treatment at Screening (use of AChEI or memantine, no use of AChEI or memantine)
- Vitamin E use at Screening (0-400 IU/day, >400 IU/day)

8.2.13 Interim Analyses

The independent eDMC will routinely evaluate unblinded safety analyses of all trial subjects while the initial 104-week trial is blinded. Additional safety analyses may be conducted throughout the trial as requested by the eDMC. The sponsor will be unblinded after completion of the initial 104-week trial.

8.2.14 Compliance/Medication Adherence

In this study, as part of the routine recording of the amount of study treatment taken by each subject, the number of tablets remaining in study packaging will be counted, reviewed, and recorded at regular intervals. These results will be used to calculate subject compliance. A day within the study will be considered an "On-Therapy" day if the subject takes one tablet.

For a subject who is followed for the entire study period, the "Number of Days Should be on Therapy" is the total number of days from the subject's first dose to the last scheduled day for treatment administration for that subject. For a subject who discontinued from the study permanently, the "Number of Days Should be on Therapy" is the total number of days from the subject's first dose to the date of the last dose of study medication.

For each subject, percent compliance will then be calculated using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Days on Therapy}}{\text{Number of Days Should be on Therapy}} \times 100.$$

Summary statistics will be provided on percent compliance by treatment group for the FAS population.

8.2.15 Extent of Exposure

Basic summary statistics for the number of doses taken by timeframe (e.g., 0-3 months, 4-6 months) as well as overall, will be provided by treatment group. Cumulative measures of exposure (e.g., Took at least 1 dose, Took at least 30 doses) will also be provided by treatment group.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 10.

Table 10 Product Descriptions

Product Name & Potency	Dosage Form
MK-8931 12 mg	tablet
MK-8931 40 mg	tablet

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Medication will be provided in bottles.

At the visits specified in the Trial Flow Chart (Section 6), the site will dispense medication using the IVRS/IWRS system. The site may provide a 'calendar sleeve' that wraps around itself and can slide up and down the bottle to expose the medication label as required. The pull off tab on the 'calendar sleeve' offers a visual reminder to help subjects/caregiver take their trial medication. The intention of the sleeves is to assist the subject/caregiver/trial partner to remember when the subject missed a dose. The sponsor will provide the sleeve to the sites and site personnel will slide them onto each bottle.

Additional instructions regarding the calendar sleeves will be provided to sites.

When the subject/caregiver/trial partner returns to the clinical site, a physical pill count will be utilized for drug accountability and recorded in the eCRF.

9.3 Clinical Supplies Disclosure

The emergency unblinding call center will use the randomization schedule for the trial to unblind subjects and to unmask treatment identity. The emergency unblinding call center should only be used in cases of emergency (see Section 7.1.4.2). In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic randomization system (IVRS/IWRS) should be used in order to unblind subjects and to unmask treatment/vaccine identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

Treatment identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the subject.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

In order to align with regional standard medical practice, trial sites in Japan are allowed to dispense subjects' treatment kits between drug dispensing visits identified in the protocol. Study medication will continue to be dispensed using the Interactive Voice Response System; however, study sites may increase the frequency with which study medication is dispensed to study participants in order to follow institutional regulations and/or local standard of care. All trial sites using partial dispensing options must follow the Merck guidance provided in the "Procedure for Investigational Medicinal Product (IMP) Management" document.

9.5 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

9.6 Standard Policies

Trial site personnel will have access to a central electronic randomization system (IVRS/IWRS system) to allocate subjects, to assign drug to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number and e-mail address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and

- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC member that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and

all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The

investigator must consult with and obtain written approval by the Sponsor prior to discarding trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided by the Sponsor.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of

the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D.Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types

Trial Visit (continuing from the initial 104-week trial; Part I)	**Visit 13**	**Visit 14**	**Visit 15**	**Visit 16**	**Visit 18**	**Visit 20**	**Visit 22**	**Visit 24**
Scheduled Week (based on date of randomization in initial 104-week trial; Part I)	108	117	130	156	208	260	312	364
Blood Parameter	Approximate Blood Volume (mL)							
Hematology	2	2	2	2	2	2	2	2
Serum/Plasma Chemistry	5	5	5	5	5	5	5	5
Expected Total (mL)	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**

12.3 Predefined Limits of Change Criteria

Table 1

Predefined Limits of Change Criteria for Laboratory Data

Laboratory Test	Criteria† as a % of a Limit of Normal Range
Hematology	
Hematocrit (M)	≤94.9% LLN
Hematocrit (F)	≤94.1% LLN
Hemoglobin (M)	≤90.5% LLN
Hemoglobin (F)	≤81.9% LLN
WBC	≤64.2% LLN
	≥149.0% ULN
Neutrophils	≤37.0% LLN
Eosinophils	≥147.0% ULN
Platelets	≤57.7% LLN
	≥177.7%ULN
Hepatic Function	
Bilirubin	≥166.7% ULN
Alkaline Phosphatase	≥300% ULN
SGOT	≥300% ULN
SGPT	≥300% ULN
Renal Function	
Creatinine	≥142.9% ULN
Clinical Chemistry	
Sodium	≤94.7% LLN
	≥105.4% ULN
Potassium	≤88.2% LLN
	≥111.1% ULN

† A laboratory value must represent a worsening from baseline (i.e., be more abnormal in the direction of interest) to meet the definition.
LLN=Lower limit of normal.
ULN=Upper limit of normal.

Table 2

Predefined Limits of Change Criteria for Vital Signs, Weight, and Temperature

Measurement	Criteria
Systolic blood pressure	≥180 mm Hg and ≥20 mm Hg increase from baseline
	≤90 mm Hg and ≥20 mm Hg decrease from baseline
Diastolic blood pressure	≥105 mm Hg and ≥15 mm Hg increase from baseline
	≤50 mm Hg and ≥15 mm Hg decrease from baseline
Pulse	≥120 bpm and ≥15 bpm increase from baseline
	≤50 bpm and ≥15 bpm decrease from baseline
Weight	≥7 % increase from baseline
	≥7 % decrease from baseline
Temperature	≥101°F and ≥2°F increase from baseline (≥38.3°C and ≥1°C increase from baseline)
Respiratory rate	> 25 or increase of ≥10 (per minute) from baseline
	< 5 or decrease of ≥10 (per minute) from baseline

Table 3

Predefined Limits of Change Criteria for ECGs

Measurement	Criteria
QTc Interval Fridericia	Prolongation compared to baseline ≥30 to ≤60 msec
	Prolongation compared to baseline >60 msec
	Value ≥500 msec

12.4 List of Abbreviations

Term	Definition
Aβ	amyloid β
AChEI	Acetylcholinesterase Inhibitors
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale Cognitive Subscale
ADCS-ADL_{MCI}	Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (Mild Cognitive Impairment version)
ADL	Activities of Daily Living
ADNI	Alzheimer's Disease Neuroimaging Initiative
AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
aMCI	Amnestic Mild Cognitive Impairment
ANCOVA	Analysis of Covariance
APOE	Apolipoprotein E
APP	Amyloid Precursor Protein
ASaT	All Subjects as Treated
ARWMC	Age-related white matter changes
AST	Aspartate aminotransferase (SGOT)
BACE	β-site APP cleaving enzyme
βhCG	β-Human Chorionic Gonadotropin
BMI	Body Mass Index
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CAC	Clinical Adjudication Committee
CAM	Confusion Assessment Method
CBC	Complete Blood Count
CCS-2D	Composite Cognition Score-2 Domain
CCS-3D	Composite Cognition Score-3 Domain
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating Sum of Boxes
CDx	Companion Diagnostic
CFB	Change from Baseline
CFR	Code of Federal Regulations
CI	Confidence Interval
cLDA	Constrained Longitudinal Data Analysis
COWAT	Controlled Oral Word Association Test;
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CVF	CERAD Verbal Fluency
CYP	Cytochrome P450
DNA	Deoxyribonucleic Acid
DMC	Data Monitoring Committee
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
DSC	Digit Symbol-Coding Test
ECG	Electrocardiogram
ECI	Events of Clinical Interest
eCRF	Electronic Case Report Form

Term	Definition
eDMC	External (to Sponsor) Data Monitoring Committee
EIA	Enzyme immunoassay
EQ-5D	EuroQol Five Dimension Questionnaire
EOC	Executive Oversight Committee
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration, USA
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
HEA	Health Economic Assessment
HLA	Human Leukocyte Antigen
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug Application; legal instrument in the USA that allows trial of unapproved, investigational new drugs in human subjects
Investigational Product	The drug, biologic, and/or device being investigated in the current trial
IRB	Institutional Review Board
IU	International Units
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LOCF	Last Observation Carried Forward
MAO	Monoamine Oxidase
MAR	Missing at Random
MCAR	Missing Completely at Random
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
MNAR	Missing Not at Random
MRI	Magnetic Resonance Imaging
mSv	millisievert
NINCDS-ADRDA	National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association
NMDA	N-Methyl-D-Aspartate
NPI	Neuropsychiatric Inventory
PD	Pharmacodynamic
PDLC	Pre-Defined Limit of Change
PET	Positron Emission Tomography
PGt	Pharmacogenetic
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/Pharmacodynamic

Term	Definition
PT	Prothrombin Time
p-tau	Phosphorylated Microtubule-Associated Protein Tau
RBC	Red Blood Cell
RNA	Ribonucleic Acid
RPE	Retinal Pigment Epithelium
RUD Lite	Resource Utilization in Dementia Lite Questionnaire
SAE	Serious Adverse Event
(S)AE	All adverse events, including serious adverse events
SAC	Scientific Advisory Committee
SAP	Statistical Analysis Plan
sAPPβ	N-terminal fragment secreted after β-secretase cleavage of APP
SGOT	Serum Glutamic Oxaloacetic Transaminase (AST)
SGPT	Serum Glutamic Pyruvic Transaminase (ALT)
siDMC	Standing Internal (to Sponsor) Data Monitoring Committee
SOC	System Organ Class
T-BIL	Total Bilirubin
TC	Telephone Contact
Term	Termination
THV	Total hippocampal volume
TSH	Thyroid Stimulating Hormone
Tx	Treatment
UGT1A1	Uridine diphosphate glucuronosyltransferase 1A1
ULN	Upper Limit of Normal
UV	Unscheduled Visit
USA	United States of America
WBC	White Blood Cell

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	SIGNATURE	DATE
_____	_____	_____

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – Assessing and Recording Adverse Events. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	SIGNATURE	DATE
_____	_____	_____