Protocol I5T-MC-AACG(d)

Assessment of Safety, Tolerability, and Efficacy of LY3002813 in Early Symptomatic Alzheimer's Disease

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Approval Date: 09-Oct-2018

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Confidential Information

LY3002813

Multicenter, randomized, double-blind, placebo-controlled, Phase 2 study comparing up to 1400 mg of LY3002813 with placebo over 76 weeks in approximately 250 patients with early symptomatic AD.

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Amendment (a) Electronically Signed and Approved by Lilly: 30 October 2017
Amendment (b) Electronically Signed and Approved by Lilly: 12 December 2017
Amendment (c) Electronically Signed and Approved by Lilly: 21 May 2018
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on approval date provided below.

Please note that strikethroughs used in Appendix 7 do not indicate redacted content but instead describe content removed during a protocol amendment.

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1. Synopsis

Title of Study:
Protocol I5T-MC-AACG(d). Assessment of Safety, Tolerability, and Efficacy of LY3002813 in Early Symptomatic Alzheimer's Disease.

Rationale:

LY3002813 is an antibody directed at the pyroglutamate modification of the third amino acid of amyloid beta (N3pG Aβ) epitope that is present only in brain amyloid plaques. It is being studied for the treatment of Alzheimer's disease (AD). The mechanism of action of LY3002813 is considered to be the targeting and removal of existing amyloid plaque, which is a key pathological hallmark of AD. The clinical strategy for LY3002813 targets the N3pG Aβ specific to amyloid plaque in the population of early symptomatic AD patients with existing brain amyloid load, as measured using the amyloid plaque biomarker, florbetapir F18 positron emission tomography (PET) imaging. This rationale is based on the amyloid hypothesis of AD, which states that the production and deposition of Aβ is an early and necessary event in the pathogenesis of AD (Selkoe 2000). Clinical support for this hypothesis comes from the demonstration that parenchymal Aβ levels are elevated before the appearance of symptoms of AD, and supported by genetic variants of AD that overproduce brain Aβ and genetic variants that protect against Aβ production (Jonsson et al. 2012; Fleisher et al. 2015). Furthermore, early in the disease, the presence of brain amyloid appears to increase the risk of conversion from mild cognitive impairment (MCI) to AD dementia (Doraiswamy et al. 2012). This suggests that enhanced clearance of Aβ will lead to slowing of AD progression.

Study I5T-MC-AACG (AACG) is a Phase 2, double-blind, placebo-controlled, study to evaluate the safety and efficacy of N3pG antibody (LY3002813) in patients with early symptomatic AD (prodromal AD and mild dementia due to AD). Study AACG will assess whether removal of existing amyloid plaque can slow the progression of disease as assessed by clinical measures and biomarkers of disease pathology and neurodegeneration over up to 72 weeks of treatment.

Multiple biomarkers of disease progress will also be evaluated. The biomarker florbetapir F18 is a PET ligand that binds to fibrillar amyloid plaque. This biomarker can provide a qualitative and quantitative measurement of brain plaque load in patients with prodromal AD or mild AD dementia. The absence of significant florbetapir F18 signal on a visual read indicates that those patients clinically manifesting cognitive impairment have sparse to no amyloid plaques. As such, implementation of florbetapir F18 will provide a screening tool for entry into the clinical trial and provide a confirmation of amyloid pathology. Florbetapir F18 PET also provides quantitative assessment of fibrillar amyloid plaque in the brain and can assess amyloid plaque reductions from the brain by LY3002813.

Alzheimer's disease progression is also associated with cerebral tauopathy, which will be assessed by flortaucipir F18 PET scans, a cortical marker of paired helical filaments. Brain atrophy, as an indicator of neurodegeneration, will be assessed by volumetric resonance imaging (vMRI).

The patient population for the clinical trial is selected to be AD patients with early symptomatic disease defined both clinically (prodromal to mild AD dementia) and by biomarkers (low to medium tau burden, plus amyloid plaque presence). The 2018 NIA-AA draft AD research framework (Alzheimer's Association 2017a) proposes that AD is defined by its underlying pathophysiologic processes which can be documented in vivo by biomarkers (such as tau and amyloid PET) or by post-mortem examination. This framework will enable a more precise approach to therapeutic intervention trials where specific pathways can be targeted at specific points in the disease process and to the appropriate people (Alzheimer's Association 2017b). Clinical-pathological correlations also strongly suggest that baseline imaging that allows staging on the basis of neurofibrillary tangles could substantially improve the power of clinical trials aimed at changing the rate of progression of the disease (Qian et al. 2017). An early AD population defined clinically and pathologically is anticipated to be more homogeneous than populations defined without tau PET, and will be sufficiently early to respond to treatments prior to more advanced irreversible neuronal loss.

Objective(s)/Endpoints:

Primary Objective	Primary Endpoint
To test the hypothesis that LY3002813 administered for up to 72 weeks will decrease the cognitive and/or functional decline in patients with early symptomatic AD	Change in cognition and function as measured by the change in integrated Alzheimer's Disease Rating Scale (iADRS) score from baseline to 18 months
Secondary Objectives To assess the effect of LY3002813 vs. placebo on clinical progression in patients with early symptomatic AD	**Secondary Endpoints** Change in cognition from baseline to 18 months as measured by: • the change in Alzheimer's Disease Assessment Scale—Cognitive subscale (ADAS-Cog_{13}) score • the change in Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) score • the change in Mini-Mental State Examination (MMSE) score • the change in Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living scale (ADCS-iADL) score
To assess the effect of LY3002813 vs. placebo on brain amyloid deposition	Change in brain amyloid plaque deposition from baseline through 18 months as measured by florbetapir F18 PET scan
To assess the effect of LY3002813 vs. placebo on brain tau deposition	Change in brain tau deposition from baseline to 18 months as measured by flortaucipir F18 PET scan
To assess the effect of LY3002813 vs. placebo on brain volume measures	Change in volumetric MRI measures from baseline to 18 months.
Safety Objective	**Safety Endpoints**
To evaluate safety and tolerability of LY3002813	• Standard safety assessments: o spontaneously reported adverse events (AEs) o clinical laboratory tests o vital sign and body weight measurements o 12-lead electrocardiograms (ECGs) o physical and neurological examinations • MRI (amyloid-related imaging abnormalities [ARIAs] and emergent radiological findings) • Columbia Suicide Severity Rating Scale (C-SSRS)

Summary of Study Design:

Study AACG is a multicenter, randomized, double-blind, placebo-controlled, Phase 2 study of LY3002813 in subjects with early symptomatic AD. The 133-week study includes a screening

period of up to 9 weeks, a treatment period of up to 72 weeks with final evaluations occurring 4 weeks later at Week 76, and a 48-week immunogenicity and safety follow-up period.

Treatment Arms and Duration:

Patients will receive the following treatments for up to 72 weeks:

- **LY3002813**: intravenous LY3002813 (700 mg Q4WK for the first 3 doses, then 1400 mg Q4WK) for up to 72 weeks or
- **Placebo**: intravenous placebo Q4WK for up to 72 weeks.

Approximate Number of Patients:

Screened – 1497

Randomized – 266

Statistical Analysis:

All efficacy analyses will follow the intent-to-treat (ITT) principle unless otherwise specified. An ITT analysis is an analysis of data by the groups to which subjects are assigned by random allocation, even if the subject does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. Unless otherwise noted, all pairwise tests of treatment effects will be conducted at a 2-sided alpha level of 0.05; 2-sided confidence intervals (CIs) will be displayed with a 95% confidence level.

Efficacy:
The primary objective of this study is to test the hypothesis that intravenous infusion of LY3002813 will slow the cognitive and/or functional decline of AD as measured by the composite measure iADRS compared with placebo in patients with early symptomatic AD. The change from baseline score on the iADRS at each scheduled postbaseline visit during the treatment period will be analyzed using an MMRM model, which includes the following terms: baseline score, pooled investigator, treatment, visit, treatment-by-visit interaction, baseline-by-visit interaction, concomitant AChEI and/or memantine use at baseline (yes/no), and age at baseline. The primary time point for treatment comparison will be at the end of the double blind treatment period (Week 76). The treatment group contrast in least-squares mean progression and its associated p-value and 95% CI will be calculated for the treatment comparison of LY3002813 vs. placebo. In addition, Bayesian posterior probability of the active treatment arm being superior to placebo by at least a margin of interest (25% slowing of placebo progression) will also be calculated.

Change from baseline at each scheduled postbaseline visit during the treatment period in secondary efficacy outcomes, including ADAS-Cog13, ADCS-iADL, CDR-SB, and MMSE, will be analyzed using the same MMRM model described for the primary analysis.

Safety:
Safety will be assessed by summarizing and analyzing AEs, laboratory analytes, vital signs, MRI scans, ECGs, immunogenicity during the double-blind treatment period.

Pharmacokinetics/Pharmacodynamics:
Compartmental modeling of LY3002813 PK data using nonlinear mixed effects modeling or other appropriate software may be explored, and population estimates for clearance and central volume of distribution may be reported. Depending on the model selected, other PK parameters may also be reported. Exploratory graphical analyses of the effect of dose level or demographic factors on PK parameters may be conducted. If appropriate, data from other studies of LY3002813 may be used in this analysis.

Pharmacokinetic/pharmacodynamic (PK/PD) relationships between plasma LY3002813 concentration and SUVr, cognitive endpoints, ARIA incidence rate or other markers of PD activity may be explored graphically. The relationship between the presence of antibodies to LY3002813 and PK, PD, safety and/or efficacy may be assessed graphically. If warranted, additional analysis may be explored to evaluate potential interactions for ADA, PD and other endpoints (PET scan, ARIA-E, etc.). Additional modeling may be performed based on the results of the graphical analyses.

2. Schedule of Activities

Schedule of Activities Protocol - I5T-MC-AACG Visit 1 (Screening Period)

Period: / Procedure	
Visit No.:	**V1**
End of Week Relative to Study Medication Start[a]	**Wk -9 through Wk -1**
Tolerance Interval for Visit (days)[a,b]	**63**
PRELIMINARY SCREENING	
Entry and Administrative	
Abbreviated (or full) Informed Consent – participant and study partner[c]	X
Patient number assigned via IWRS	X
Demographics and habits	X
Entry Diagnostics	
MMSE[c,d,s]	X
CBB[c]	X
SCREENING	
Full Informed Consent – participant and study partner[d]	X
Inclusion/exclusion review	X
Physical/neurological examination[e]	X
Previous/concomitant medications	X
Preexisting conditions	X
Entry Diagnostics	
MHIS	X
Safety Assessments	
Vital signs[f]	X
Height and weight[g]	X
ECG in triplicate[h]	X
C-SSRS/SHSF/SHFU[i,j]	X
Laboratory Specimens	
Human chorionic gonadotropin (HCG) (if applicable)[k,l,m]	X[b]
Clinical chemistry, hematology	X[b]
High sensitivity C-reactive protein	X
HBsAg[n]	X
HCV RNA PCR[o]	X
Urinalysis	X
Screening PET Scans and MRI	
Flortaucipir F18 PET scan[l,p]	X
MRI[q]	X
Florbetapir F18 PET scan[b,m,r]	X

Schedule of Activities, Protocol I5T-MC-AACG, Visit 1 (Screening Period) Abbreviations and Footnotes

Abbreviations: Aβ = amyloid β; CBB = CogState Brief Battery; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation visit; HBsAg = hepatitis B surface antigen; HCG = human chorionic gonadotropin; HCV = hepatitis C virus; IWRS = interactive web response system; MHIS = Modified Hachinski Ischemia Scale; Examination; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; No. = number; PCR = polymerase chain reaction; PET = positron emission tomography; SHSF = Self-Harm Supplement form; SHFU = Self-Harm Follow-Up; V = visit; Wk = week.

[a] The interval between V1 and V2 may be up to 63 days to allow for completion of V1 screening procedures, assessments, and evaluation of results from laboratory tests and ECGs. V1 is not considered complete until all screening procedures have been completed and results reviewed by the investigator to determine patient eligibility. V1 may be conducted over more than 1 day. Subjects in screening at the time screening was paused are allowed to continue screening beyond the 63 days to allow for completion of V1 screening procedures; this will not be a protocol deviation. Additional details are provided in Section 5.1.1. Subjects who had completed screening but were not yet randomized at the time randomization was paused are allowed to be randomized beyond 63 days; this will not be a protocol deviation. Additional details are provided in Section 5.1.1.

[b] A florbetapir F18 PET scan is the final screening criterion for establishing patient eligibility, although the MRI may be performed after the florbetapir F18 PET scan. Patients whose screening florbetapir F18 PET scan results are not available within the 63 day screening window will remain eligible within V1 until these results become available if all other eligibility criteria have been met. Note: If a patient's screening florbetapir F18 PET scan result confirming eligibility for the study has not been received by the site by Day 63 of the screening period, then repeat the following laboratory tests: blood hematology, chemistry, and serum pregnancy test (HCG) for women of childbearing potential (WOCBP). Results of the repeated labs are to be reviewed by the investigator or qualified designee for assessment of the patient's continued eligibility. Repeat screening for MMSE, CBB, C-SSRS, ECG, flortaucipir F18 PET, MRI, and laboratory testing for HBsAg and HCV RNA PCR is not required. V1 is not considered complete until all screening procedures have been completed and results reviewed by the investigator or qualified designee to determine patient eligibility.

[c] A preliminary screening informed consent may be obtained to conduct initial screening to collect demographics data and administer the MMSE and CBB. Patients who do not meet the MMSE screening criteria are not to have any other screening procedures performed with the exception of the CBB. The CBB should be administered to all patients at the screening visit, regardless of the MMSE score. They may be rescreened for the MMSE 8 weeks after the first screen. Study partners are not required to complete the preliminary screening informed consent.

[d] Patients who meet the MMSE screening criteria may proceed to the remaining screening procedures once they have given signed/dated informed consent for the full study and their study partner has given signed/dated informed consented to participate as a study partner.

[e] A complete physical and neurological exam is to be performed at this visit. Additional details are provided in Section 9.4.1.

[f] Sitting blood pressure and pulse will be measured after 5 minutes in the sitting position only. Temperature will be collected with sitting vital signs.

[g] Height and weight will be measured with shoes removed.

[h] ECGs should be taken in triplicate at approximately 1-minute intervals. ECGs should be collected at approximately the same time of day, as much as possible, to minimize diurnal variation.

[i] The baseline version of the C-SSRS is to be administered at V1. Patients at imminent risk of suicide (positive response to question 4 or 5 on the C-SSRS) will be excluded from participating in the study.

[j] The SHSF is completed after each C-SSRS administration to enter the number of discrete events of suicidal behavior identified. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, then the SHFU form will be used to collect additional information to allow for a more complete assessment of these behaviors.

[k] Females of childbearing potential are to have a serum pregnancy test (HCG) at V1 (if applicable).

[l] Females of childbearing potential are to have a urine pregnancy test (HCG) on the day of flortaucipir F18 PET imaging before the flortaucipir F18 dose is administered.

[m] Females of childbearing potential are to have a urine pregnancy test (HCG) on the day of florbetapir F18 PET imaging before the florbetapir F18 dose is administered.

[n] Patients with a past history of Hepatitis B are to have a serum HBsAg test at screening V1 and are excluded if the HBsAg test is positive.

[o] Patients with a past history of Hepatitis C are to have a HCV RNA PCR test at screening V1 and are excluded if the HCV RNA PCR test is positive.

[p] A screening flortaucipir F18 PET scan will be performed as part of the study eligibility criteria at all sites to determine patient eligibility for participation in Study AACG (see Appendix 5). With the exception of an MRI and a florbetapir F18 PET scan, a patient should meet all other V1 eligibility criteria before having a screening flortaucipir F18 PET scan. The flortaucipir F18 PET scan will be submitted to a centralized PET imaging vendor designated by Lilly for an assessment of patient's eligibility. A historical flortaucipir F18 PET scan may be submitted to be considered for eligibility if performed within 6 months of V1.

[q] A local screening MRI will be performed at V1 as part of the study eligibility criteria. With the exception of the evidence of amyloid pathology by florbetapir F18 PET scan, a patient should meet all other V1 eligibility criteria before having an MRI scan. The MRI scans will be reviewed by the investigator or qualified designee for immediate patient management. After the MRI scan is read locally, the scan is to be submitted to the centralized MRI vendor designated by Lilly for final determination of MRI eligibility. Results of centrally read MRIs will be used for data analysis and report-writing purposes and patient safety and eligibility will be reported back to sites.

[r] A screening florbetapir F18 PET scan will be performed as part of the study eligibility criteria to determine patient eligibility for participation in Study AACG (see Appendix 6). With the exception of an MRI, a patient should meet all other V1 eligibility criteria before having a screening florbetapir F18 PET scan. The PET scan will be submitted to a centralized PET imaging vendor designated by Lilly for assessment of patient's eligibility. The florbetapir F18 PET screening criteria must be met (scan results consistent with the presence of amyloid pathology) in order for the patient to proceed to V2 and be randomized to treatment assignment.

[s] Assessment is to include the audio voice recording of the rater's questions and the patient and caregiver responses to assessment questions.

Schedule of Activities, Protocol I5T-MC-AACG, Visit 2 through Visit 14 (Double-Blind Period)

Period: / Procedure	Rand												
Visit No.:	**V2[a,b]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**
End of Week Relative to Study Medication Start	0	4	8	12	16	20	24	28	32	36	40	44	48
Tolerance Interval for Visit (days)	0	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Inclusion/exclusion review	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IWRS – dispensation of study medication (LY3002813)	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical/neurological examination[e]	X[f]			X[f]			X[f]			X[g]			
Ophthalmological examination[h]	[j]			X[h]				X[h]					
Dermatological examination[i]	[j]			X[i]			X[i]						
Previous/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Preexisting conditions/adverse events[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
LY3002813 study medication administered[k]	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Measures													
ADAS-Cog_{13}[l,ff]	X			X			X			X			
ADCS-ADL[l,ff]	X			X			X			X			
CDR-SB[l,ff]	X			X			X			X			
MMSE[l,ff]				X			X			X			
Safety Assessment													
C-SSRS/SHSF/SHFU[m,n]	[m]	X	X	X	X	X	X	X	X	X	X	X	X

Schedule of Activities, Protocol I5T-MC-AACG, Visit 2 through Visit 14 (Double-Blind Period)

Period: / Procedure	Rand												
Visit No.:	**V2[a,b]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**
End of Week Relative to Study Medication Start	0	4	8	12	16	20	24	28	32	36	40	44	48
Tolerance Interval for Visit (days)	0	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Laboratory Specimens[o]													
Clinical chemistry, hematology[p]	X	X	X	X			X			X			
High sensitivity C-reactive protein[p]	X	X	X	X			X			X			
Urinalysis[p]	X												
Serum for anti-LY3002813 antibody[p]	X	X	X	X	X		X			X			
Serum LY3002813[q,r]	X[q]	X[r]	X[r]	X[q]	X[r]		X[q]			X[r]			
Blood for assessment of APOE genotype[p,s]	X												
Whole blood, plasma and serum for biomarker storage[p,t]	X			X			X			X			
Blood for pharmacogenomics[p,t,u]	X												
Other Safety Measures													
Weight	X			X			X			X			
Vital signs and temperature[v,w]	X[w]	X	X	X[w]	X	X	X[w]	X	X	X[w]	X	X	X
ECG in triplicate[x]	X	X	X	X			X			X			
MRI[y]	[z]	X		X[aa]	X		X			X			
Additional Efficacy Measures													
Flortaucipir F18 PET scan[bb,cc]	[z]												
Florbetapir F18 PET scan[bb,dd]	[z]						X[bb,dd]						

Schedule of Activities, Protocol I5T-MC-AACG, Visit 15 through Visit 21 (Double-Blind Period) and Follow-Up

Period: / Procedure									
Visit No.:	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**ED[c]**	**V801-V804[d,ee]**
End of Week Relative to Study Medication Start	52	56	60	64	68	72	76		88-124
Tolerance Interval for Visit (days)	±7	±7	±7	±7	±7	±7	±7		±14
Inclusion/exclusion review	X	X	X	X	X	X			
Contact IWRS – dispensation of study medications (LY3002813)	X	X	X	X	X	X			
Physical/neurological examination[e]	X[f]			X[g]			X[f]	X[f]	
Ophthalmological examination[h,j]								X[h]	
Dermatological examination[i,j]								X[i]	
Previous/concomitant medications	X	X	X	X	X	X	X	X	X
Preexisting conditions/adverse events[e]	X	X	X	X	X	X	X	X	X
LY3002813 study medication administered[k]	X	X	X	X	X	X			
Efficacy Measures									
ADAS-Cog_{13}[l,ff]	X			X			X	X	
ADCS-ADL[l,ff]	X			X			X	X	
CDR-SB[l,ff]	X			X			X	X	
MMSE[l,ff]	X			X			X	X	
Safety Assessment									
C-SSRS/SHSF/SHFU[m,n]	X	X	X	X	X	X	X	X	X

Schedule of Activities, Protocol I5T-MC-AACG, Visit 15 through Visit 21 (Double-Blind Period) and Follow-Up

Period: / Procedure									
Visit No.:	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**ED[c]**	**V801-V804[d,ee]**
End of Week Relative to Study Medication Start	52	56	60	64	68	72	76		88-124
Tolerance Interval for Visit (days)	±7	±7	±7	±7	±7	±7	±7		±14
Laboratory Specimens[o]									
Clinical chemistry, hematology[p]	X			X			X	X	
High sensitivity C-reactive protein[p]	X			X			X	X	
Urinalysis[p]	X			X			X	X	
Serum for anti-LY3002813 antibody[p]	X						X	X	X
Serum LY3002813[q,r]	X[q]			X[r]		X[q]	X[r]	X[r]	X[r]
Blood for assessment of APOE genotype[p,s]									
Whole blood, plasma and serum for biomarker storage[p,t]	X			X			X	X	
Blood for pharmacogenomics[p,t,u]									
Other Safety Measures									
Weight	X			X			X	X	
Vital signs and temperature[v,w]	X[w]	X	X	X[w]	X	X	X[w]	X[w]	X
ECG in triplicate	X			X			X	X	
MRI[y]	X						X	X	
Additional Efficacy Measures									
Flortaucipir F18 PET Scan[bb,cc]							X[bb,cc]	X[bb,cc]	
Florbetapir F18 PET scan[bb,dd]	X[bb,dd]						X[bb,dd]	X[bb,dd]	

Schedule of Activities, Protocol I5T-MC-AACG, Visit 2 through Visit 21 (Double-Blind Period) and Follow-Up Abbreviations and Footnotes

Abbreviations: Aβ = amyloid β; ADA = anti-drug antibodies; ADAS-Cog_{13} = 13-item Alzheimer's Disease Assessment Scale-Cognitive subscore; ADCS-ADL = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory; APOE = apolipoprotein subtype E; ARIA-E = amyloid related imaging abnormalities–edema/effusions; CDR-SB = Clinical Dementia Rating-Sum of Boxes; CRF = case report form; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation visit; HCG = human chorionic gonadotropin; IWRS = interactive web response system; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; No. = number; PET = positron emission tomography; SHFU = Self-Harm Follow-Up form; SHSF = Self-Harm Supplement form; TE = treatment-emergent; V = visit.

[a] Confirm that the patient has met all V1 eligibility criteria before proceeding with V2 procedures.

[b] At V2, appointments should be made for all remaining visits and should be scheduled as close as possible to the target date, relative to V2. Procedures for some visits may take more than 1 day.

[c] If a patient discontinues before the double-blind period endpoint (V21 at Week 76), complete the Early Discontinuation CRFs. The patient should be encouraged to return to the site beginning 12 weeks after the ED visit for an immunogenicity follow-up visit (V801 through V804).

[d] Patients are to return to the site for collection of blood samples and safety assessments for assessment of immunogenicity status at V801 (Week 88). Follow-up for patients experiencing clinically significant events associated with TEADA status is described in Section 9.4.7.2.

[e] Any clinically significant changes from baseline on follow-up physical/neurological examinations should be noted on the AE page.

[f] A complete physical and neurological exam is to be performed at this visit. Additional details are provided in Section 9.4.1.

[g] A brief physical and neurological exam is to be performed at this visit. Additional details are provided in Section 9.4.1.

[h] Ophthalmological examinations will be performed only in patients who previously received LY3202626/oral placebo in this study. The final examination for each patient will be the next scheduled ophthalmological examination after the final administration of LY3202626/oral placebo. It will not be considered a protocol deviation if this examination is scheduled sooner than indicated above in order to accommodate patient and/or site preference. Patients who received LY3202626/oral placebo after their V9 ophthalmological examination are to have an unscheduled ophthalmological examination at the next available opportunity. These examinations must be conducted by an ophthalmologist or optometrist (where permitted by law). Additional details are provided in Section 9.4.6.3.

[i] Dermatological examinations will be performed only in patients who previously received LY3202626/oral placebo in this study. The final examination for each patient will be the next scheduled dermatological evaluation after the final administration of LY3202626/oral placebo. It will not be considered a protocol deviation if this examination is scheduled sooner than indicated above in order to accommodate patient and/or site preference. Patients who received LY3202626/oral placebo after their V8 dermatological examination are to have an unscheduled dermatological examination at the next available opportunity. These examinations must be conducted by a dermatologist. Additional details are provided in Section 9.4.6.4.

[j] For subjects randomized prior to amendment (d), the ophthalmological and dermatological examination performed at screening will serve as the baseline ophthalmological and dermatological examination.

[k] Study drug will be administered by intravenous administration at investigative study site. Patients should be observed for approximately 2 hours following each infusion of LY3002813 for the first 6 infusions. After the first six doses, a minimal post-infusion observation time of 60 minutes will be required for all subsequent infusions. However, patients who have had dosing restarted after ARIA-E are required to be monitored for 2 hours following infusion for a minimum of 3 subsequent infusions, and a minimum of 60 minutes post-infusion observation thereafter.

[l] When administered, cognitive and functional assessments (ADAS-Cog_{13}, ADCS-ADL, CDR, and MMSE) should be performed first, before medical procedures that could be stressful for the patient (e.g., blood draws).

[m] The C-SSRS administered at screening will serve as the baseline C-SSRS.

[n] The 'since last visit' version of the C-SSRS will be administered at visits after V2 (Week 0) to the patient with the study partner/study informant present, after the cognitive and functional assessments. The SHSF is completed after each C-SSRS administration to enter the number of discrete events of suicidal behavior identified. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, then the SHFU form will be used to collect additional information to allow for a more complete assessment of these behaviors

[o] Unscheduled laboratory tests may be performed at the discretion of the investigator.

[p] Labs are to be collected prior to administration of the intravenous study medication (LY3002813 or IV placebo). Record the date and times of sample collection on the Lab Requisition Form.

[q] **Pre-dose** (before beginning the infusion) samples for intravenous study medication (LY3002813) may be collected from the intravenous site prior to beginning the infusion. **Post-dose** (within 30 minutes of completion of the infusion) samples for intravenous study medication (LY3002813) should be collected from the arm that did not receive the infusion at V2 (Week 0), V5 (Week 12), V8 (Week 24), V15 (Week 52), and V20 (Week 72).

[r] A single pre-dose LY3002813 sample should be collected before beginning the infusion at V3 (Week 4), V4 (Week 8), V6 (Week 16), V11 (Week 36), and V18 (Week 64). In addition, a single sample for serum LY3002813 should be collected at V21 (Week 76), or ED, and V801 (visits at which the patient may not receive a study drug infusion). If LY3002813 infusion is permanently discontinued but the patient remains in the study, one PK sample should be collected at the soonest scheduled visit regardless if serum LY3002813 is on the Schedule of Activities at that visit. Subsequent PK sample collection should follow the protocol Schedule of Activities for serum LY3002813 collection unless the scheduled visit exceeds 6 months since discontinuation of infusions. No additional serum collection for LY3002813 is required once the patient exceeds 6 months since discontinuation of LY3002813 infusions. Record the actual date and times of sample collection on the Lab Requisition Form.

[s] A blood sample will be collected to determine APOE genotype. The APOE genotype sample may be collected at an alternative visit if it cannot be collected at V2.

[t] Blood for biomarker storage, and blood for pharmacogenomic samples are to be collected unless not allowed or unfeasible due to local regulations prohibiting sample transport outside of the country.

[u] Pharmacogenomic samples may be collected at an alternative visit if they cannot be collected at V2. It will not be a protocol deviation if a biomarker storage sample cannot be collected for technical reasons (e.g., if the site is unable to collect enough blood via venipuncture).

[v] Sitting blood pressure and pulse will be measured after 5 minutes in the sitting position at **all** visits. Temperature will be collected with sitting vital signs.

[w] In addition, orthostatic blood pressure and pulse will be measured at V2 (Week 0), V5 (Week 12), V8 (Week 24), V11 (Week 36), V15 (Week 52), V18 (Week 64), V21 (Week 76), or ED, and at unscheduled visits after 5 minutes in the supine position and after 3 minutes standing.

[x] Electrocardiograms should be taken in triplicate at approximately 1-minute intervals. ECGs should be collected at approximately the same time of day, as much as possible, to minimize diurnal variation. ECGs are to be performed prior to the administration of intravenous study medication (LY3002813 and IV placebo).

[y] If MRI is done on the same day as cognitive and functional assessments, then it should be done after cognitive and functional tests. MRI may be done before other visit procedures, including cognitive and functional tests, but in that case must be done at least 1 day before other visit procedures.

[z] The screening flortaucipir F18 PET scan, MRI, and florbetapir F18 PET scan done at V1 serve as the baseline flortaucipir F18 PET scan, MRI, and florbetapir F18 PET scan, respectively.

[aa] The V5 MRI is to be performed 2 weeks prior to the V5 (Week 12) LY3002813 infusion to allow for receipt and review of the central vendor MRI report prior to a possible LY3002813 dose change at V5 (Week 12).

bb Females of childbearing potential are to have a urine pregnancy test (HCG) performed on the day of florbetapir F18 PET and flortaucipir F18 PET imaging before the florbetapir F18 dose or flortaucipir F18 dose is administered to confirm that they are not pregnant.

cc All patients will have a flortaucipir F18 PET scan done at V21 (Week 76) or ED (if ED occurs more than 36 weeks after randomization) (see Appendix 5). Before the flortaucipir F18 PET scan, the investigator should review the patient's medical history and concomitant medications to verify there is no risk factor for torsades de pointes and review the most recent ECG. If clinically meaningful abnormalities are noted on the ECG, the advisability of the flortaucipir scan should be considered by the investigator in consultation with the Lilly-designated medical monitor. ***The study investigator and site clinical study team will not have access to the flortaucipir F18 follow-up scans, as the site clinical study team must remain blinded to any potential changes in tau deposition.***

dd All patients will have double-blind period florbetapir F18 PET scans done at V8 (Week 24), V15 (Week 52), and V21 (Week 76) or ED (if ED occurs more than 8 weeks after a florbetapir F18 PET scan has been performed at a previous visit) (see Appendix 6). ***The study investigator and site clinical study team will not have access to any florbetapir F18 follow-up scans, as the site clinical study team must remain blinded to any potential changes in amyloid deposition.***

ee Patients are to return to the site for an immunogenicity and safety follow-up visit (V801) at Week 88 (or 12 weeks after the ED visit) for collection of blood samples for anti-drug antibody (ADA) measurements and assessment of adverse events and concomitant medications. The need for additional study visits after V801 will be determined by results of the ADA sample taken at V801. A patient will stop immunogenicity follow-up visits when they either complete 3 additional quarterly visits (Week 100, Week 112, and Week 124) or complete a visit at which their ADA returns to baseline (2-fold titer from baseline), whichever occurs first. See Section 5.1.3 and Section 9.4.7.2 for details.

ff Assessment is to include the audio voice recording of the rater's questions and the patient and caregiver responses to assessment questions.

3. Introduction

3.1. Study Rationale

LY3002813 is an antibody directed at the pyroglutamate modification of the third amino acid of amyloid beta (N3pG Aβ) epitope that is present only in brain amyloid plaques. It is being studied for the treatment of Alzheimer's disease (AD). The mechanism of action of LY3002813 is considered to be the targeting and removal of existing amyloid plaque, which is a key pathological hallmark of AD. The clinical strategy for LY3002813 targets the N3pG Aβ specific to amyloid plaque in the population of early symptomatic AD patients with existing brain amyloid load, as measured using the amyloid plaque biomarker, florbetapir F18 positron emission tomography (PET) imaging. This rationale is based on the amyloid hypothesis of AD, which states that the production and deposition of Aβ is an early and necessary event in the pathogenesis of AD (Selkoe 2000). Clinical support for this hypothesis comes from the demonstration that parenchymal Aβ levels are elevated before the appearance of symptoms of AD, and supported by genetic variants of AD that overproduce brain Aβ and genetic variants that protect against Aβ production (Jonsson et al. 2012; Fleisher et al. 2015). Furthermore, early in the disease, the presence of brain amyloid appears to increase the risk of conversion from mild cognitive impairment (MCI) to AD dementia (Doraiswamy et al. 2012). This suggests that enhanced clearance of Aβ will lead to slowing of AD progression.

Study I5T-MC-AACG (AACG) is a Phase 2, double-blind, placebo-controlled study to evaluate the safety and efficacy of N3pG antibody (LY3002813) in patients with early symptomatic AD (prodromal AD and mild dementia due to AD). Study AACG will assess whether removal of existing amyloid plaque can slow the progression of disease as assessed by clinical measures and biomarkers of disease pathology and neurodegeneration over up to 72 weeks of treatment.

Multiple biomarkers of disease progress will also be evaluated. The biomarker florbetapir F18 is a PET ligand that binds to fibrillar amyloid plaque. This biomarker can provide a qualitative and quantitative measurement of brain plaque load in patients with prodromal AD or mild AD dementia. The absence of significant florbetapir F18 signal on a visual read indicates that those patients clinically manifesting cognitive impairment have sparse to no amyloid plaques. As such, implementation of florbetapir F18 will provide a screening tool for entry into the clinical trial and provide a confirmation of amyloid pathology. Florbetapir F18 PET also provides quantitative assessment of fibrillar amyloid plaque in the brain and can assess amyloid plaque reductions from the brain by LY3002813.

Alzheimer's disease progression is also associated with cerebral tauopathy, which will be assessed by flortaucipir F18 PET scan, a cortical marker of paired helical filaments. Brain atrophy, as an indicator of neurodegeneration, will be assessed by volumetric resonance imaging (vMRI).

The patient population for the clinical trial is selected to be AD patients with early symptomatic disease defined both clinically (prodromal to mild AD dementia) and by biomarkers (low to medium tau burden, plus amyloid plaque presence). The 2018 NIA-AA draft AD research

framework (Alzheimer's Association 2017a) proposes that AD is defined by its underlying pathophysiologic processes which can be documented in vivo by biomarkers (such as tau and amyloid PET) or by post-mortem examination. This framework will enable a more precise approach to therapeutic intervention trials where specific pathways can be targeted at specific points in the disease process and to the appropriate people (Alzheimer's Association 2017b). Clinical-pathological correlations also strongly suggest that baseline imaging that allows staging on the basis of neurofibrillary tangles could substantially improve the power of clinical trials aimed at changing the rate of progression of the disease (Qian et al. 2017). An early AD population defined clinically and pathologically is anticipated to be more homogeneous than populations defined without tau PET, and will be sufficiently early to respond to treatments prior to more advanced irreversible neuronal loss.

3.2. Background

Alzheimer's disease is an age-related neurodegenerative disorder characterized by progressive decline in cognitive function and the ability to perform activities of daily living, ultimately resulting in dementia, typically with fatal complications. The amyloid hypothesis of AD postulates that the accumulation of amyloid-β peptide (Aβ) is an early and necessary event in the pathogenesis of AD. This hypothesis suggests that treatments that slow the accumulation of Aβ plaque in the brain or increase clearance of Aβ may be able to slow the progression of the AD clinical syndrome. The other hallmark neuropathological lesion of AD, intraneuronal neurofibrillary tangles consisting of tau proteins, is thought to be another marker for disease progression (Braak and Braak 1996). The relationship between these 2 pathologies is still unclear, although the presence of both is necessary for the diagnosis of definite AD.

Converging evidence from both genetic at-risk and age at-risk cohorts suggests that the pathophysiological process of AD begins well more than a decade before the clinical stage now recognized as AD dementia, and that neurodegeneration is already apparent on magnetic resonance imaging (MRI) by the stage of MCI. Like many disorders, AD occurs on a continuum from asymptomatic (preclinical) to MCI, then to dementia in mild, moderate, and severe stages. Recent clinical trial results in mild-to-moderate AD dementia, as well as evidence from transgenic animal experiments, suggest that treating AD during the earlier stages could have the greatest potential benefit on the disease and its progression, particularly when considering therapies targeted at Aβ reduction (Doody et al. 2014; Fleisher et al. 2015; Siemers et al. 2016).

3.2.1. LY3002813 Nonclinical Studies

The safety of LY3002813, a plaque-specific monoclonal antibody, was assessed in a 6-week toxicity study in cynomolgus monkeys, including evaluations of safety pharmacology and toxicokinetics. The administration of LY3002813 in monkeys of up to a maximum dose of 100 mg/kg/week (bolus intravenous [IV]) for 6 weeks resulted in no drug-related findings. Repeat-dose hazard identification studies of up to 6 months' duration were conducted in the aged PDAPP (APPV717F) transgenic mouse model of Aβ deposition to investigate potential effects related to clearance of Aβ from the brain. In addition, a specialized 3-month study to investigate the potential for cerebral amyloid angiopathy (CAA)-associated microhemorrhage was

conducted in aged PDAPP transgenic mice. These studies in the PDAPP mouse were conducted with mE8c (LSN3026818), a murine analog antibody of LY3002813, to avoid limitations due to potential immunogenicity from repeated administration of the humanized antibody to the mouse. No drug-related findings occurred in the hazard identification studies in PDAPP mice at mE8c doses of up to 100 mg/kg/week (the highest dose tested). Treatment of PDAPP mice with mE8c at 12.5 mg/kg/week for 3 months did not exacerbate CAA-associated microhemorrhage at a dose that produced a maximum pharmacological response (reduction in deposited brain Aβ) in these animals. See the Investigator's Brochure (IB) for details regarding nonclinical LY3002813 studies.

3.2.2. LY3002813 Phase 1 Studies

The first human dose study of LY3002813 was I5T-MC-AACC (Study AACC). Study AACC was a Phase 1, patient- and investigator-blind, randomized within cohort, placebo-controlled, parallel-group, single-dose followed by multiple-dose, dose-escalation study in patients with MCI due to AD or mild-to-moderate AD to assess the safety, tolerability, pharmacodynamics (PD), and pharmacokinetics (PK) of single and multiple IV doses of LY3002813. The study included Japanese and non-Japanese patients. Patients with AD were enrolled into the single-ascending dose (SAD) phase and were each administered a single IV dose of LY3002813 (5 dosing cohorts from 0.1 mg/kg IV to 10 mg/kg IV) or placebo followed by a 12-week follow-up period for each dose level. After the follow-up period, the same patients proceeded into the multiple-ascending dose (MAD) phase (5 cohorts) and were administered IV doses of LY3002813 (0.3 mg/kg IV to 10 mg/kg IV; subjects in the 0.1 mg/kg SAD cohort received 0.3 mg/kg in the MAD phase) or placebo approximately once per month for up to 4 doses, depending on the initial dose level. This phase concluded with a 12-week follow-up period. The relative exposure assessment of an unblinded single subcutaneous (SC) dose of 3 mg/kg LY3002813 in AD patients was also performed, followed by a 12-week follow-up assessment. The PK of an unblinded single IV dose of 1 mg/kg LY3002813 in young, healthy male subjects was assessed to determine whether the absence of the amyloid target affected the PK as compared with amyloid-positive AD patients.

After single-dose administration from 0.1 mg/kg to 3.0 mg/kg, the mean terminal elimination half-life was approximately 4 days, increasing to approximately 10 days (243 hours) at the 10-mg/kg dose level. The PK of a single dose of 1.0 mg/kg IV LY3002813 in young, healthy subjects was indistinguishable from the PK in AD patients at the same dose level.

In AACC, florbetapir F18 scans were performed at baseline and after the last MAD, separated by approximately 7 months, to assess the PD effects of LY3002813. The change from baseline in grey matter standardized uptake value ratio (SUVr) with cerebellum as a reference region was compared across dose cohorts. There was a highly significant reduction from baseline in cerebral amyloid by PET at the highest dose, 10 mg/kg ($p<.0002$). The analysis showed consistent reduction in cortical amyloid among these patients who received 3 to 5 doses of 10 mg/kg LY3002813. The mean observed reduction in florbetapir F18 PET signal corresponds to a mean 50% reduction in total brain fibrillar amyloid. Meaningful target engagement (amyloid reduction) was likely not achieved at doses smaller than or equal to 3 mg/kg IV every

4 weeks (Q4W) because of the rapid elimination of LY3002813 and the lack of sustained exposure.

I5T-MC-AACD (Study AACD) is an ongoing Phase 1b single- and multiple-dose study to assess the safety, tolerability, PK, and PD of single and multiple IV doses of LY3002813 in patients with mild cognitive impairment due to AD or mild to moderate Alzheimer's dementia. It is evaluating up to 150 patients in 6 different dosing cohorts receiving single, every 2 weeks, or every 4 weeks dosing of either 10 mg/kg, 20 mg/kg or 40 mg/kg of LY3002813. Treatment durations being assessed include single dose, six month dosing every two weeks, or up to 72 weeks of every 4 week dosing. Safety, PK and PD data from this ongoing study are used to inform further development of LY3002813. See Section 3.3 and the IB for detailed safety and PK information regarding LY3002813.

3.3. Benefit/Risk Assessment

3.3.1. Benefit

There is a large unmet medical need for disease-modifying treatments for AD. Data from the completed Phase 1a Study AACC and from the ongoing Phase 1b Study AACD indicate a dramatic reduction in cerebral amyloid (as assessed by florbetapir F18 PET imaging) in individuals who received repeated doses of at least 10 mg/kg (IB; Fleisher et al. 2018). Along with assessment of safety and tolerability of LY3002813, this study will assess whether removal of existing amyloid plaque will show evidence of slowed clinical decline and change in biomarkers of disease progression relative to placebo treatment.

Although there are currently no available disease-modifying agents for the treatment of AD, there are several medications approved by the Food and Drug Administration (FDA) and Health Canada for the treatment of symptoms of AD; these include acetylcholinesterase inhibitors (e.g., donepezil, galantamine, and rivastigmine) and the N-methyl D-aspartate receptor antagonist memantine. Because these medications are considered standard of care for the treatment of AD, participants in this trial will be permitted to take these medications during the course of the study, provided that they have been on a stable dose at the time of randomization and remain on a stable dose throughout the study.

3.3.2. Risks

Potential risks (discussed below) for LY3002813 include, but are not limited to, formation of anti-drug antibodies (ADA), hypersensitivity (immediate and non-immediate, including infusion-related reactions), and amyloid-related imaging abnormalities (ARIA).

Anti-Drug Antibodies: High incidences of treatment-emergent anti-drug antibodies (TEADAs) have been observed in clinical studies with LY3002813. Although there were no serious adverse events (SAEs) related to the development of ADAs in Study AACC, the incidence of TEADAs in LY3002813-exposed patients and subjects was >90%; in Study AACD, the incidence of TEADAs to date (final protocol) in LY3002813-exposed patients and subjects is approximately 75%. In AACD, on 10 mg/kg Q2WK dosing, one patient was observed with a highly elevated

ADA titer of 1:163840 on Day 144 postbaseline, with no clinical consequences. Anti-drug antibodies levels may affect PD levels of drug effect. Infusion reactions and ADAs are potential risks common to all large molecules. See the IB for details regarding TEADAs.

As a high prevalence of ADAs was observed in Study AACC, a risk management plan for immune safety will be incorporated into the clinical trial including a protocol for management of infusion reactions, and standardized data collection for infusion reaction AEs.

Hypersensitivity (Immediate and Non-immediate, including infusion-related reactions): There is a risk of an infusion-related reaction with LY3002813 therapy. In Study AACC, AEs of mild or moderate infusion reactions were reported in 6 of 37 patients with AD who received multiple IV doses of LY3002813 and in 0 of the 6 healthy volunteers. In AACD one patient receiving 10 mg/kg IV every 2 weeks had a mild infusion-related reaction and 2 mild injection site reactions. To mitigate the risk of hypersensitivity (immediate and non-immediate), including infusion-related reactions, specific study exclusion criteria related to allergy are defined in the clinical protocol; guidance regarding use of premedications and slowing or stopping the LY3002813 infusion is provided in Sections 9.4.7.1.1 and 9.4.7.1.2, respectively; and a protocol for management of infusion reactions is included in the trial Manual of Operations.

Amyloid-Related Imaging Abnormalities: Some anti-amyloid therapies designed to remove amyloid have been associated with ARIA–edema/effusions and –hemorrhage/hemosiderin deposition (ARIA-E and ARIA-H; also known as vasogenic edema and cerebral microhemorrhage, respectively) (Sperling et al. 2011). These abnormalities are best detected on an MRI using fluid attenuation inversion recovery (FLAIR) sequences for ARIA-E and the T2* gradient-recalled echo for ARIA-H.

Potential symptoms of ARIA-E include headache, gait instability, dizziness, tremor, worsening cognitive function, alteration of consciousness, seizures, unsteadiness, and vomiting (Ostrowitzki et al. 2012; Sperling et al. 2012). However, ARIA-E can also be unaccompanied by any symptoms.

Microhemorrhages and superficial siderosis (ARIA-H) are often associated with ARIA-E and both are thought to be possibly related to removal of vascular Aβ or amyloid trafficking at the blood–brain barrier (Ketter et al. 2017). Moreover, ARIA-H are believed to indicate a higher risk for macrohemorrhage as well as for the presence of significant cerebral amyloid angiopathy. While ARIA does occur during the natural course of AD, there appears to be an increased risk of microhemorrhage with anti-amyloid antibody treatment in preclinical models and ARIA-H and ARIA-E in humans (e.g., bapineuzumab, gantenerumab, aducanumab [Black et al. 2010]) as well.

In Study AACC, two cases of asymptomatic ARIA-H, but no ARIA-E were detected by MRI. In the ongoing study AACD 42 subjects received up to 13 doses of LY3002813 (~32 subjects) or placebo (~10 subjects) as of 03 August 2017. Of these, one mildly symptomatic and four asymptomatic cases of ARIA-E, and 5 events of ARIA-H in 4 patients (including in 3 patients who also experienced ARIA-E) have been reported. Two cases occurred in subjects dosed with 10 mg/kg Q2WK, 2 occurred in subjects who received a single dose of 20 mg/kg, and one in a

patient who received 10 mg/kg Q4WK. There was no clear relationship to APOE4 carrier status, ADA, PK or PD in these cases. All ARIA-E resolved without clinical consequence after treatment discontinuation, except for one patient with asymptomatic ARIA-E that was ongoing on MRI as of 10 August 2017.

To mitigate the potential risk of ARIA-H and ARIA-E during treatment with LY3002813, a dose titration regimen will be employed utilizing an initial dose that has lower risk of ARIA-E prior to increasing to full study dose. In addition, a dose reduction algorithm will be employed for incident ARIA during the trial (see Section 7.4.1). No cases of ARIA will have dose-reintroduction if permanent dose discontinuation rules (described in Section 8.1) are met.

To further aid in mitigation of potential risks of ARIA-H and ARIA-E during treatment with LY3002813, the current study includes a screening MRI scan that will be used to exclude patients with preexisting ARIA-E, >4 microhemorrhages or more than one area of superficial siderosis. In addition to scheduled MRIs, unscheduled MRIs may to be obtained at the discretion of the investigator upon suspicion of ARIA. It is recommended to repeat MRIs approximately every 4 to 6 weeks until resolution of ARIA-E or stabilization of incident ARIA-H is documented.

Further guidance for management of ARIA-E and incident ARIA-H is provided in the Operations Manual and the protocol includes guidance on dose reduction (Section 7.4.1), temporary treatment discontinuation (Section 8.1.1, permanent treatment discontinuation (Section 8.1), and continued safety monitoring and treatment options (Section 9.4.7.4).

3.3.3. Benefit/Risk Assessment Summary

To mitigate the potential risks described in Section 3.3.2, the current study will include standard safety assessments; i.e., reported AEs, clinical laboratory tests, immunogenicity assessments, vital sign and body weight measurements, 12-lead electrocardiograms (ECGs), and physical examinations.

Additional safety assessments will include neurological examinations (as part of each physical examination), MRI examinations, and suicidality evaluations using the Columbia-Suicide Severity Rating Scale (C-SSRS). The current study will use an independent external Data Monitoring Committee (DMC) to monitor data on an ongoing basis to ensure the continuing safety of patients enrolled in this study.

The current study includes placebo as a comparator, and approximately one-half of the patients will be randomized to placebo. In addition, all patients participating in the study will have a designated study partner who will have regular contact with the patient, accompany the patient to study visits, and liaise with the study staff between visits as needed (see Section 6.1 for additional information about the role of the study partner).

In conclusion, the available non-clinical and clinical data support the intravenous administration of LY3002813 to the intended study population according to the proposed clinical investigation plan and also provide a sufficient margin of safety for the proposed design and doses. There are

currently no disease-modifying treatments for AD. The potential benefits of LY3002813 showing disease-modifying properties in AD are considered to outweigh the potential risks.

More information about the known and expected benefits, risks, SAEs and reasonably anticipated AEs of LY3002813 are to be found in the IB.

4. Objectives and Endpoints

Table AACG.4.1 shows the objectives and endpoints of the study.

Table AACG.4.1. Objectives and Endpoints

Primary Objective	Primary Endpoint
To test the hypothesis that LY3002813 administered for up to 72 weeks will decrease the cognitive and/or functional decline in patients with early symptomatic AD	Change in cognition and function as measured by the change in integrated Alzheimer's Disease Rating Scale (iADRS) score from baseline to 18 months
Secondary Objectives To assess the effect of LY3002813 vs. placebo on clinical progression in patients with early symptomatic AD	**Secondary Endpoints** Change from baseline to 18 months as measured by: • the change in Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog_{13}) score • the change in Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) score • the change in Mini Mental State Examination (MMSE) score • the change in Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living scale (ADCS-iADL) score
To assess the effect of LY3002813 vs. placebo on brain amyloid deposition	Change in brain amyloid plaque deposition from baseline through 18 months as measured by florbetapir F18 PET scan
To assess the effect of LY3002813 vs. placebo on brain tau deposition	Change in brain tau deposition from baseline to 18 months as measured by flortaucipir F18 PET scan
To assess the effect of LY3002813 vs. placebo on brain volume measures	Change in volumetric MRI measures from baseline to 18 months.

Safety Objective	**Safety Endpoints**
To evaluate safety and tolerability of LY3002813	• Standard safety assessments: o spontaneously reported adverse events (AEs) o clinical laboratory tests o vital sign and body weight measurements o 12-lead ECGs o physical and neurological examinations • MRI (ARIA and emergent radiological findings) • Columbia Suicide Severity Rating Scale (C-SSRS)
Exploratory Objectives	**Exploratory Endpoints**
To assess the effect of LY3002813 vs. placebo on clinical progression in patients with early symptomatic AD	• the change in dependence level derived from ADCS-ADL scale scores
To assess peripheral PK and presence of anti-LY3002813 antibodies over 72 weeks	• Plasma Pharmacokinetics of LY3002813 • Anti-drug-antibodies (ADA) against LY3002813 including treatment-emergent ADA and neutralizing antibodies.

5. Study Design

5.1. Overall Design

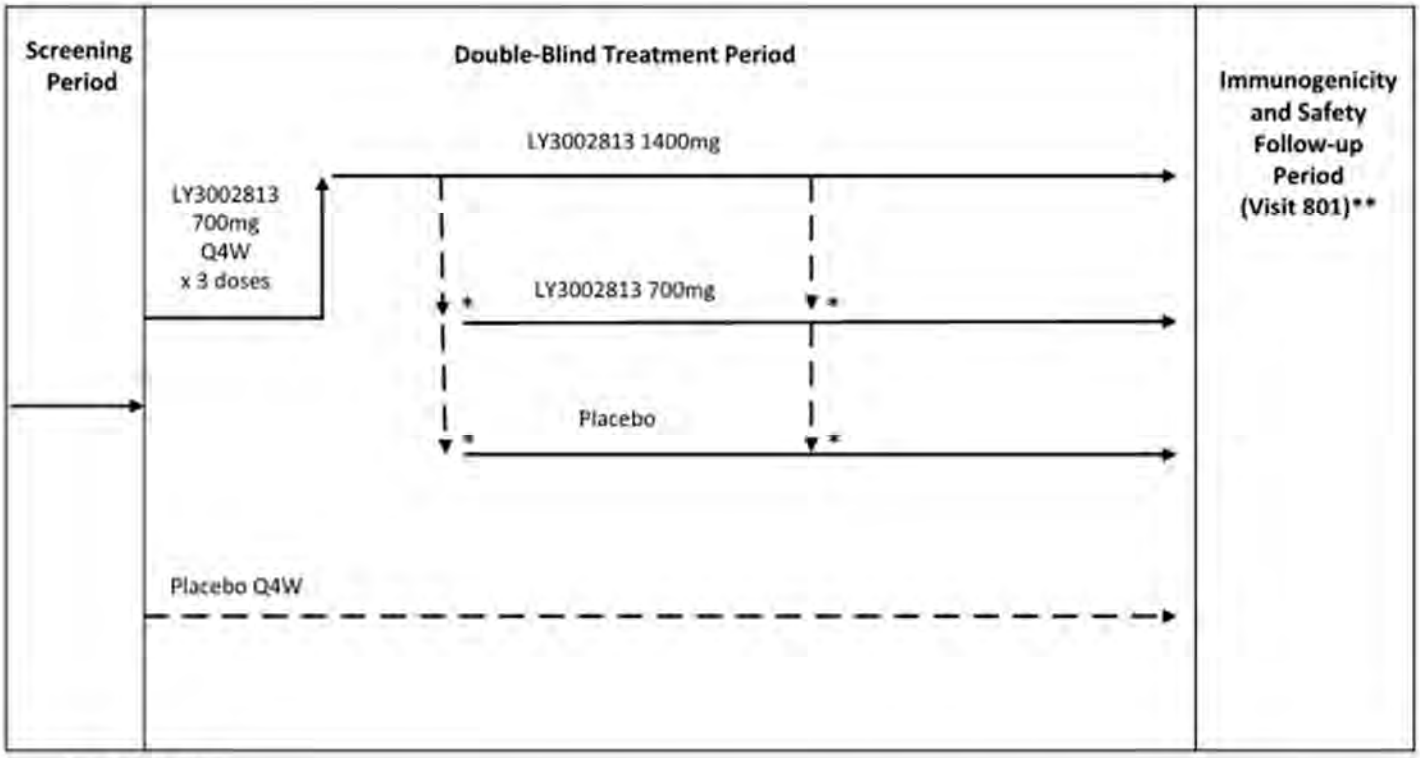
Study AACG is a multicenter, randomized, double-blind, placebo-controlled, Phase 2 study of LY3002813 in subjects with early symptomatic AD. The 133-week study includes a screening period of up to 9 weeks, a treatment period of up to 72 weeks with final evaluations occurring 4 weeks later at Week 76, and a 48-week immunogenicity and safety follow-up period. Subjects who meet entry criteria will be randomized in a 1:1 ratio to one of the following treatments:

- **LY3002813**: IV LY3002813 (700 mg Q4WK for the first 3 doses, then 1400 mg Q4WK) for up to 72 weeks or
- **Placebo**: IV placebo Q4WK for up to 72 weeks.

The primary hypothesis being tested is that LY3002813 administered for up to 72 weeks will result in a significant slowing in cognitive/functional decline compared with placebo as measured by the change from baseline to the end of the double blind treatment period (Week 76) on the integrated Alzheimer's Disease Rating Scale (iADRS), in subjects with early symptomatic AD (where early symptomatic AD refers to the combination of 2 stages: prodromal AD [MCI-AD] and mild AD dementia; Alaka et al. 2015).

Under previous versions of this protocol, LY3002813 was administered in combination with LY3202626, an inhibitor of β-site amyloid precursor protein cleaving enzyme (BACE)1. However, as of this amendment (d), the combination therapy and the oral placebo have been discontinued from the study.

Abbreviations and definitions are provided in Appendix 1; clinical laboratory tests are described in Appendix 2; Study governance considerations are described in detail in Appendix 3; and Hepatic monitoring tests for treatment-emergent abnormality is provided in Appendix 4.



* At 6 and 12 month florbetapir PET scans, dosing decision to continue LY3002813 1400mg Q4W or reduce to LY3002813 700mg Q4W or placebo
**Additional study visits after V801 may be required. See Section 5.1.3 and Section 9.4.7.2 for details
Q4W = once every 4 weeks

Figure AACG.5.1. Illustration of study design for Clinical Protocol I5T-MC-AACG.

5.1.1. Screening Period (Visit 1)

At or before Visit 1, the study will be explained to the patient (and his or her legal representative, if applicable) and study partner. Informed consent must be obtained before any study procedures are conducted. The screening period spans the time between Visit 1 to Visit 2. Study assessments are shown in the Schedule of Activities (Section 2).

A preliminary screening informed consent may be obtained to conduct initial screening to collect demographics data and administer the Mini-Mental State Examination (MMSE) and CogState Brief Battery (CBB). Patients who do not meet the MMSE screening criteria are not to have any other screening procedures performed with the exception of the CBB. The CBB should be administered to all patients at the screening visit, regardless of the MMSE score. They may be rescreened for the MMSE 8 weeks or more after the first screen (see Section 6.4). Patients who screen failed on the CBB in the previous version of this protocol may be reconsented and immediately rescreened using the MMSE (see Section 6.4).

Patients who meet the MMSE screening criteria may proceed to the remaining screening procedures once they have given signed/dated informed consent for the full study.

Once the MMSE criteria are met, 63 days are allowed for completion of Visit 1 screening assessments, procedures, and evaluation of results from laboratory tests, ECGs, physical and neurological examination, flortaucipir F18 PET, MRI, and florbetapir F18 PET. Even though florbetapir F18 PET imaging may be the last screening procedure of the study, it is expected that the centrally read florbetapir F18 PET results will be available within the timeframe of 63 days. However, it will not be a protocol deviation should the screening florbetapir F18 PET results not be available until after 63 days.

Patients whose screening florbetapir F18 PET results are not available until after 63 days will remain eligible within Visit 1 until these results become available. **Note:** If a patient's screening florbetapir F18 PET results confirming evidence of amyloid burden are received by the site after 63 days, laboratory tests (blood hematology, chemistry, and serum human chorionic gonadotropin [HCG] for females of childbearing potential) are to be repeated for that patient. Results of the repeated labs are to be reviewed by the investigator or qualified designee for assessment of the patient's continued eligibility. Repeat screening for MMSE, CBB, C-SSRS, ECG, flortaucipir F18 PET imaging, and MRI, and laboratory testing for hepatitis B surface antigen (HBsAg) and hepatitis C virus (HCV) RNA polymerase chain reaction (PCR), is not required.

Patients in active screening prior to implementation of amendment (d) remain eligible within Visit 1 until all screening procedures are completed and results are available. This will not be a protocol deviation. Patients who complete Visit 1 beyond 63 days are to repeat laboratory tests (blood hematology, chemistry, and serum HCG for females of childbearing potential) prior to being randomized. The results of these laboratory tests are to be reviewed by the investigator or qualified designee for assessment of the patient's continued eligibility. Repeat screening for MMSE, CBB, C-SSRS, ECG, flortaucipir F18 PET imaging, MRI, and laboratory testing for HBsAg and HCV RNA PCR is not required.

Visit 1 is not considered complete until all screening procedures have been completed, results have been reviewed by the investigator or qualified designee, and the investigator or qualified designee has confirmed that the patient is eligible to be randomized. Only then can the patient proceed to Visit 2.

Current or planned use of concomitant medications, the effects of vacations or absences on protocol compliance, and general compliance with the protocol will be discussed at Visit 1. Patients must meet eligibility criteria (Section 6.1 and Section 6.2) to continue to Visit 2. Patients who do not meet all inclusion criteria or who meet any exclusion criteria may be discontinued from the study.

5.1.1.1. Screening Procedures

Screening entry and administrative procedures, cognitive assessments, safety assessments, and laboratory assessments (see Schedule of Activities in Section 2) are to be done at Visit 1 before the screening flortaucipir F18 PET scan, MRI, and florbetapir F18 PET scan procedures.

5.1.1.1.1. Modified Hachinski Ischemic Scale (MHIS)

The Modified Hachinski Ischemic Scale (MHIS) will be completed at Visit 1 to exclude patients likely to have dementia of vascular etiology. The MHIS (Hachinski et al. 1975) is an 8-item scale that examines clinical features that may be consistent with vascular dementia and is commonly used as a screening tool to exclude patients with multi-infarct dementia from entrance into clinical trials assessing neuropsychopharmacologic therapy in patients with AD. The scale is completed by the physician based on clinical information obtained from diagnostic information and physical examination. The scale takes about 10 to 15 minutes to complete, depending on the availability of the data needed. Scores for the 8 items are added together for a total score. Patients who score ≥4 are more likely to have a dementia of vascular etiology and are excluded from participating in the trial.

5.1.1.1.2. Mini-Mental State Examination (MMSE)

The MMSE will be administered to patients at Visit 1 to determine if the patient meets entry criteria for cognitive impairment. The MMSE is a brief instrument used to assess cognitive function in patients (Folstein et al. 1975). The MMSE should be administered by the same rater from visit to visit to reduce potential variability. The instrument is divided into 2 sections. The first section measures orientation, memory, and attention. The maximum score for the first section is 21. The second section tests the ability of the patient to name objects, follow verbal and written commands, write a sentence, and copy figures. The maximum score for the second section is 9. The range for the total MMSE score is 0 to 30, with lower scores indicating great level of impairment.

5.1.1.1.3. CogState Brief Battery

The CBB is a brief (15-18 minute), computer-based cognitive test battery designed to measure psychomotor function, attention, working memory, and memory (Maruff et al. 2009, 2013; Fredrickson et al. 2010; Darby et al. 2012). The CBB has been shown to be sensitive to AD-related cognitive decline in healthy older adults and in adults with amnestic MCI (Darby et

al. 2002, 2012; Lim et al. 2013a, b) as well as to improvement in cognition arising from treatment with cognitive-enhancing drugs (Davison et al. 2011; Jaeger et al. 2011; Nathan et al. 2013). The CBB will be administered at Visit 1 to better understand the utility of this test in assessment of cognitive impairment, but patient eligibility will not depend on the CBB results to determine if the patient meets the cognitive criteria for the study. The CBB will be administered to patients at Visit 1 after administration of the MMSE regardless of whether the patient meets MMSE entry criteria. Prior to performing the screening CBB, patients must perform a practice CBB to familiarize themselves with the instrument.

5.1.1.1.4. Columbia Suicide Severity Rating Scale – Adult Version

The C-SSRS will be administered to patients at Visit 1 to assess psychological health. The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the corresponding assessment period. The C-SSRS, included here as a screening assessment, is described in detail in Section 9.4.6.1. The C-SSRS "Baseline" version will be used at screening, and the findings will constitute the baseline assessment. Patients at imminent risk of suicide (positive response to question 4 or 5 on the C-SSRS) will be excluded from participating in the study.

The C-SSRS will be administered to the subject after the cognitive assessments. Responses from subject will be considered when administering the scale. The Self-Harm Supplement form (SHSF) will be completed after each C-SSRS administration to enter the number of discrete events of suicidal behavior identified. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, then the Lilly Self-Harm Follow-Up form will be used to collect additional information to allow for a more complete assessment of these behaviors.

5.1.1.1.5. Screening Positron Emission Tomography and Magnetic Resonance Imaging

All other screening criteria should be met in order for the patient to proceed with flortaucipir F18 PET scan, followed by MRI, and a florbetapir F18 PET scan procedure.

5.1.1.1.5.1. Screening Flortaucipir F18 PET Scan

A screening flortaucipir F18 PET scan will be performed as part of the study eligibility criteria (see Appendix 5). The flortaucipir F18 PET scan will be submitted to a centralized PET imaging vendor designated by Lilly for assessment of patient's eligibility.

A historical flortaucipir F18 PET scan may be submitted to be considered for eligibility if the PET scan was performed within 6 months of Visit 1. If a historical flortaucipir PET scan is deemed acceptable for meeting entry criteria, then the MMSE, which is still to be administered at Visit 1, will serve as the baseline MMSE for statistical analyses, but will **not** be used for meeting entry criteria.

The flortaucipir F18 PET screening criteria should be met (scan results consistent with sponsor-derived eligibility limits for flortaucipir F18 PET) before the patient can undergo the MRI and florbetapir F18 PET scan.

Specific instructions for the flortaucipir F18 PET scan itself will be provided in the PET Imaging Manual.

5.1.1.1.5.2. Screening MRI

A local screening MRI will be performed at Visit 1 as part of the study eligibility criteria. With the exception of the evidence of amyloid pathology by florbetapir F18 PET scan, a patient should meet all other Visit 1 eligibility criteria before having an MRI. The MRI scans will be reviewed by the investigator or qualified designee for immediate patient management. After the MRI scan is read locally, the scan is to be submitted to the centralized MRI vendor designated by Lilly for final determination of MRI eligibility. Results of centrally read MRIs will be used for data analysis and report-writing purposes and patient safety and eligibility will be reported back to sites.

5.1.1.1.5.3. Screening Florbetapir F18 PET Scan

A screening florbetapir F18 PET scan will be performed as part of the study eligibility criteria (see Appendix 6). With the exception of the MRI, a patient should meet all other Visit 1 eligibility criteria before having a screening florbetapir F18 PET scan. The florbetapir F18 PET scan will be submitted to a centralized PET imaging vendor designated by Lilly for assessment of patient's eligibility.

The florbetapir F18 PET screening criteria must be met (scan results consistent with sponsor-derived eligibility limits for amyloid plaque pathology) in order for the patient to proceed to Visit 2 and be randomized to treatment assignment.

Specific instructions for the florbetapir F18 PET scan itself will be provided in the PET Imaging Manual.

5.1.2. Double-Blind Period (Visit 2 through Visit 21)

The treatment period is a double-blind treatment phase beginning at Visit 2. At Visit 2, appointments should be made for all remaining visits and should be scheduled as close as possible to the target date, relative to Visit 2. Patients who meet entry criteria will be enrolled and randomized to receive up to 72 weeks of treatment with LY3002813 or placebo.

Every 4 weeks during this treatment period, all patients will be administered IV study medication (placebo or LY3002813) onsite as an IV infusion of approximately 140 mL over a minimum of 30 minutes, and assessments will be made.

Final endpoint measures and safety assessments for the double-blind period will be performed at Visit 21 (Week 76) 4 weeks following the patient's last dose of study medication. See the Schedule of Activities (Section 2) for the timing of events and the measures to be assessed. Procedures for some visits may take more than 1 day.

The study investigator and site clinical study team will not have access to any florbetapir F18 and flortaucipir F18 follow-up PET scans, as the investigator and site clinical study team must remain blinded to any potential changes in amyloid deposition.

5.1.3. Immunogenicity and Safety Follow-up Visits (Visits 801 through 804)

Patients are to return to the site for an immunogenicity and safety follow-up visits (Visit 801 through Visit 804) beginning at Week 88 (or 12 weeks after their last dose of LY3002813) for collection of blood samples for anti-drug antibody (ADA; anti-LY3002813 antibody) and PK measurement, assessment of adverse events, C-SSRS, concomitant medications, and vital signs.

A patient will continue to return to the site for quarterly immunogenicity and safety follow-up visits (V802 [Week 100], V803 [Week 112], and V804 [Week 124]) until the patient completes V804 or the site is notified that the patient meets criteria for discharge from immunogenicity and safety follow-up, whichever occurs first (see Section 9.4.7.2 for details). See the Schedule of Activities (Section 2) for the timing of events and the measures to be assessed.

5.2. Number of Participants

Approximately 266 participants will be randomized.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last patient.

5.4. Scientific Rationale for Study Design

Continuing Standard of Care. Patients may take AD symptomatic medications such as concomitant acetylcholinesterase inhibitors (AChEIs) and/or memantine and/or Axona if such medications are standard of care (SOC) in the patient's country and have been given for at least 4 months and stable dosing has been maintained for at least 2 months before Visit 2. During the double-blind treatment period (V2 to V21), changes in doses of available symptomatic medications for MCI or AD will require reporting to the sponsor and these changes should occur only when necessary for the adequate overall care of the patient. The effect of LY3002813 treatment plus SOC will be compared with placebo plus SOC.

Dosing. As described more fully in Section 7.1, LY3002813 (700 mg or 1400 mg) will be administered every 4 weeks as an IV infusion of approximately 140 mL over a minimum of 30 minutes.

Design. Study AACG is a multicenter, randomized, double-blind, placebo-controlled study of LY3002813 in patients with early symptomatic AD (where early symptomatic AD refers to the combination of 2 stages: prodromal AD [MCI-AD] and mild AD dementia) (Alaka et al. 2015). The study is intended to characterize the benefits and risks of treatment with LY3002813 versus placebo in patients early symptomatic AD.

Study AACG includes a placebo treatment arm and allows all patients to continue their AD standard of care concomitant medications. Inclusion of a placebo treatment arm is acceptable in Study AACG because there are no available disease-modifying treatments for AD; this approach is in agreement with the use of placebo described in the Declaration of Helsinki (World Medical

Association 2013). The use of a placebo comparator in Study AACG is needed to determine efficacy and safety of LY3002813 therapy.

The study includes a screening visit, which can last up to 63 days, at which patients are required to have PET flortaucipir F18 PET and florbetapir F18 PET imaging results consistent with tau and amyloid pathology in order to be randomized to the double-blind period. The duration of the double-blind period of the study is 76 weeks and includes up to 72 weeks of treatment, with endpoint measures and safety assessments at the end of the double-blind treatment period (Week 76), to assess the safety, tolerability and efficacy of LY3002813 versus placebo.

In addition to AE reporting, safety measures such as laboratory assessments, immunogenicity testing, vital signs and weight monitoring, ECG monitoring, physical examinations, neurological examinations, MRI assessments, and assessments of suicidal ideation and behavior are included to facilitate a comprehensive safety evaluation. For patients enrolled under previous versions of this protocol, which included a combination arm of LY3002813 (N3pG) and LY3202626 (BACE inhibitor-IV), final dermatological examinations by a dermatologist and final comprehensive ophthalmological examinations by an ophthalmologist or optometrist (where permitted by law) will be performed at the next visit occurring after the patient stopped receiving LY3202626/oral placebo.

5.5. Justification for Dose

LY3002813 doses of 700 mg and 1400 mg administered intravenously once every 4 weeks were selected based on current preclinical pharmacology and toxicology data and clinical PK, PD, and safety data. Prior and ongoing exposures include 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg, 20 mg/kg, and 40 mg/kg in single and/or multi-dose dosing schedules. Data from Study AACC and AACD suggested that PK of LY3002813 is linear when the dose is not less than 10 mg/kg. Mean half-life was about 9-11 days when dose is ≥10 mg/kg, so minimal accumulation in plasma PK was predicted for 700 mg and 1400 mg Q4 week IV dosing. High levels of florbetapir F18 PET signal reductions were seen with a single dose of 20 mg/kg, and were comparable to florbetapir F18 PET reductions seen with a 10 mg/kg Q2 week dosing schedule at 3 months (see Section 3.2 and the IB for details). Based on this as well as decreased patient burden with an every 4 week dosing schedule compared with an every 2 week dosing schedule and comparable safety (see Section 3.3), 1400 mg Q4 week dosing was selected as the highest dose regimen for robust amyloid plaque lowering. As noted in Section 3.3.2, the lowest rate of ARIA-E has been observed with 10 mg/kg monthly dosing. For this reason, a titration schedule (700 mg Q4 week for the first 3 doses, then 1400 mg Q4 week) is proposed to reduce ARIA incidence while enabling patients to achieve high PD effects. In addition, dose reduction rules have been established for incident ARIA-E (see Section 7.4.1).

6. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

6.1. Inclusion Criteria

Patients are eligible for enrollment in the study only if they meet all of the following criteria:

Type of Patient and Disease Characteristics

[1] Gradual and progressive change in memory function reported by patients or informants for ≥ 6 months.

[50] [Note: Criterion #50 has been replaced by criterion #59.]

[59] An MMSE score of 20 to 28 (inclusive) at Visit 1 or an acceptable historical flortaucipir PET scan within 6 months prior to Visit 1 that meets the central read criteria.

[51] Meet flortaucipir F18 scan (central read) criteria.

[52] Meet florbetapir F18 scan (central read) criteria.

Patient/Subject Characteristics

[2] Men or women, 60 to 85 years of age, inclusive, at the time of informed consent.

[3] Contraception

a. Male subjects

i. Male subjects, regardless of their fertility status, with non-pregnant female partners of childbearing potential must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms as well as one additional highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine devices) or effective method of contraception (such as diaphragms with spermicide or cervical sponges) for 90 days after study drug dosing.

ii. Men and their partners may choose to use a double–barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. Thus, each barrier method must include use of a spermicide. It should be noted, however, that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined.

iii. Male subjects with pregnant partners should use condoms during intercourse for the duration of the study and until the end of estimated relevant potential exposure in women of childbearing potential, predicted to be 90 days following last dose of study drug.

iv. Male subjects should refrain from sperm donation for the duration of the study and until 90 days following last dose of study drug.

v. Male subjects who are in exclusively same sex relationships (as their preferred and usual lifestyle) are not required to use contraception.

b. Women

i. Women of childbearing potential (WOCBP) must be using or willing to use two forms of effective contraception (e.g., combined oral contraceptive, intrauterine device, spermicide), for the duration of their participation in the trial and for an additional 3 months after their participation ends or

ii. Women not of childbearing potential are defined as those who are:

a) Infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation),

b) Post-menopausal – defined as either

i) A woman 55 or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or

ii) A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

iii. All female patients of child-bearing potential must test negative for pregnancy at Visit 1 based on serum pregnancy test.

[4] Have a study partner who will provide written informed consent to participate, is in frequent contact with the patient (defined as at least 10 hours per week), and will accompany the patient to study visits or be available by telephone at designated times.

A second study partner may serve as backup. The study partner(s) is/are required to accompany the patient for signing consent. One study partner is requested to be present on all days the C-SSRS/Self-Harm Supplement Form is administered and must be present on all days the cognitive and functional scales are administered (i.e., Visits 1, 2, 5, 8, 11, 15, 18, and 21/early discontinuation [ED]). If a patient has a second study partner, it is preferred that one study partner be primarily responsible for the CDR and ADCS-ADL assessments. If a study partner(s) is not able to accompany the patient in person for visits other than those listed above, they must be available by telephone for the following assessments:

- AEs and concomitant medications
- relevant portions of the C-SSRS/Self-Harm Supplement Forms

If a study partner must withdraw from study participation, a replacement may be allowed at the investigator's discretion. The replacement will need to sign a separate informed consent on the first visit that he/she accompanies the patient to participate.

Study partners must be able to communicate with site personnel and be willing to comply with protocol requirements, and in the investigator's opinion must have adequate literacy to complete the protocol-specified questionnaires.

[5] Have adequate premorbid literacy, vision, and hearing for neuropsychological testing in the opinion of the investigator.

[6] Have given written informed consent approved by Lilly and the ethical review board (ERB) governing the site.

[7] Are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria:

Medical Conditions

[8] Have a Modified Hachinski Ischemia Scale (MHIS; Hachinski et al. 1975) score of ≥4.

[9] Lack, in the investigator's opinion, of adequate premorbid literacy, adequate vision, or adequate hearing to complete the required psychometric tests.

[10] Significant neurological disease affecting the central nervous system (CNS), other than AD, that may affect cognition or ability to complete the study, including but not limited to, other dementias, serious infection of the brain, Parkinson's disease, multiple concussions, or epilepsy or recurrent seizures (except febrile childhood seizures).

[11] Current serious or unstable illnesses including cardiovascular, hepatic, renal, gastroenterologic, respiratory, endocrinologic, neurologic (other than AD), psychiatric, immunologic, or hematologic disease and other conditions that, in the investigator's opinion, could interfere with the analyses in this study; or has a life expectancy of <24 months.

[12] History of cancer within the last 5 years, with the exception of non-metastatic basal and/or squamous cell carcinoma of the skin, in situ cervical cancer, non-progressive prostate cancer, or other cancers with low risk of recurrence or spread.

[13] Patients with any current primary psychiatric diagnosis other than AD if, in the judgment of the investigator, the psychiatric disorder or symptom is likely to confound interpretation of drug effect, affect cognitive assessment, or affect the patient's ability to complete the study. [Patients with history of schizophrenia or other chronic psychosis are excluded.]

[14] Have a history of long QT syndrome.

[15] Are clinically judged by the investigator to be at serious risk for suicide as assessed by medical history, examination, or the C-SSRS.

[16] [Note: Criterion #16 has been replaced by criterion #57.]

[57] [Note: Criterion #57 has been deleted.]

[17] History of alcohol or drug use disorder (except tobacco use disorder) within 2 years before the screening visit.

[18] [Note: Criterion #18 has been deleted.]

[19] Have a history of clinically significant multiple or severe drug allergies, or severe post-treatment hypersensitivity reactions (including but not limited to erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, and/or exfoliative dermatitis).

[20] Known positive serologic findings for human immunodeficiency virus (HIV) antibodies. Local laws and regulations may apply to whether testing is required.

Magnetic Resonance Imaging, Vital Signs, Electrocardiograms, Laboratory Tests, and Physical Examination

[21] Have any clinically important abnormality at screening, as determined by investigator, in physical or neurological examination, vital signs, ECG, or clinical laboratory test results that could be detrimental to the patient, could compromise the study, or show evidence of other etiologies for dementia.

[22] Screening MRI which shows evidence of significant abnormality that would suggest another potential etiology for progressive dementia or a clinically significant finding that may impact the patient's ability to safely participate in the study.

[23] Have any contraindications for MRI, including claustrophobia or the presence of contraindicated metal (ferromagnetic) implants/cardiac pacemaker.

[24] [Note: Criterion #24 has been replaced by criterion #58.]

[58] Have a centrally read MRI demonstrating presence of ARIA-E, >4 cerebral microhemorrhages, more than 1 area of superficial siderosis, any macrohemorrhage or severe white matter disease.

[25] An average (ECG in triplicate) corrected QT (QTcF) interval measurement >450 msec (men) or >470 msec (women) at screening (as determined at the investigational site). The site may request a central read prior to making determination of this criterion.

[26] [Note: Criterion #26 has been replaced by criterion #53.]

[53] Patients with a past history of Hepatitis B should have HBsAg testing at screening and are excluded if HBsAg is positive.

[27] [Note: Criterion #27 has been replaced by criterion #54.]

[54] Patients with past history of Hepatitis C should have HCV RNA PCR testing at screening and are excluded if HCV RNA PCR is positive.

[28] Calculated creatinine clearance <30 mL/min (Cockcroft-Gault formula; Cockcroft and Gault 1976) at screening.

[29] Alanine transaminase (ALT) ≥2X the upper limit of normal (ULN) of the performing laboratory, aspartate aminotransferase (AST) ≥2X ULN, total bilirubin level (TBL) ≥1.5X ULN, or alkaline phosphatase (ALP) ≥1.5X ULN at screening.

NOTE: Patients with TBL ≥1.5X ULN are not excluded if they meet all of the following criteria for Gilbert syndrome:

1. Bilirubin is predominantly indirect (unconjugated) at screening (direct bilirubin within normal limits).
2. Absence of liver disease.
3. ALT, AST, and ALP ≤1X ULN at screening.
4. Hemoglobin is not significantly decreased at screening.

Prior/Concomitant Therapy

[30] Have received treatment with a stable dose of an acetylcholinesterase inhibitor (AChEI) and/or memantine for less than 2 months before randomization. [If a patient has recently stopped an AChEI and/or memantine, he or she must have discontinued treatment at least 2 months before randomization.]

[31] Changes in concomitant medications that could potentially affect cognition and their dosing should be stable for at least 1 month before screening, and between screening and randomization (does not apply to medications discontinued due to exclusions or with limited duration of use, such as antibiotics).

[32] [Note: Criterion #32 has been deleted.]

[33] Current use of drugs known to significantly prolong the QT interval (see the Manual of Operations for a list of excluded drugs).

[34] Have had prior treatment with a passive anti-amyloid immunotherapy <5 half-lives prior to randomization.

[35] Have received active immunization against Aβ in any other study.

[36] Have known allergies to LY3002813, related compounds, or any components of the formulation; or history of significant atopy.

[37] [Note: Criterion #37 has been deleted.]

[38] Have allergies to either monoclonal antibodies, diphenhydramine, epinephrine, or methylprednisolone.

Procedural

[39] Sensitivity to florbetapir F18 or flortaucipir F18.

[40] Intend to use drugs known to significantly prolong the QT interval within 14 days or 5 half-lives, whichever is longer, of a scheduled screening/baseline flortaucipir F18 PET scan, or have a medical history of a risk factor of torsades de pointes.

[41] Poor venous access.

[42] Contraindication to MRI.

[43] Contraindication to PET.

[44] Present or planned exposure to ionizing radiation that, in combination with the planned administration of study PET ligands, would result in a cumulative exposure that exceeds local recommended exposure limits.

Prior/Concurrent Clinical Trial Experience

[45] Are currently enrolled in any other interventional clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

[46] Have participated, within the last 30 days (4 months for studies conducted in Japan; 3 months for studies conducted in the UK), in a clinical trial involving an investigational product. If the previous investigational product is scientifically or medically incompatible with this study and has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed prior to screening (Participation in observational studies may be permitted upon review of the observational study protocol and approval by the sponsor).

[47] [Note: Criterion #47 has been replaced by criterion #55.]

[55] Have previously completed or withdrawn from this study or received LY3002813 in any prior investigational study. (This exclusion criterion does not apply to patients who are allowed to rescreen before randomization in this study).

[56] [Note: Criterion #56 has been deleted.]

Other Exclusions

[48] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[49] Are Lilly employees or are employees of third-party organizations (TPOs) involved in study who require exclusion of their employees, or have study partners who are Lilly employees or are employees of TPOs involved in a study which require exclusion of their employees.

6.2.1. Rationale for Exclusion of Certain Study Candidates

The use of LY3002813 in older patients is anticipated; thus this study will specifically examine the efficacy and safety in an elderly population. Criterion [2] defines the population age range for the purposes of this study. Therefore, patients not meeting the age criterion are excluded.

6.3. Lifestyle Restrictions

1. Patients should refrain from donating blood or blood products from the time of their screening visit until 6 months following the last dose of study drug.

2. Patients should avoid excessive use of alcohol from the screening visit until the study ends. Excessive alcohol consumption is defined for men as consuming an average of more than 3 drinks per day, or more than 21 drinks per week. For women, excessive use of alcohol is defined as consuming an average of more than 2 drinks per day, or more than 14 drinks per week.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened if the screen failure is due to non-eligible imaging results. If the screen failure is due to not meeting cognitive criteria on the MMSE, then one rescreen will be allowed after 8 weeks. If a patient failed the CBB screening in the previous version of this protocol, then the patient may be reconsented and immediately rescreened using the MMSE. Other reasons for screen fail will require sponsor approval for rescreen.

7. Treatments

7.1. Treatments Administered

This study involves a comparison of LY3002813 administered as an IV infusion of approximately 140 mL over a minimum of 30 minutes compared with placebo. In the double-blind period, the treatment groups will be given an IV infusion of LY3002813 or placebo for up to 72 weeks.

Patients whose amyloid plaque reduction as measured by florbetapir F18 PET scans at Visit 8 (Week 24) and/or Visit 15 (Week 52) meet criteria will have a double-blinded dose reduction of LY3002813 to 700 mg or IV placebo, based on the specific level of florbetapir F18 PET signal at that time, for the remaining duration of the double-blind treatment period. These dose reduction rules may be modified by the sponsor based on ongoing collection of PD and safety data. If ARIA-E occurs prior to Visit 5 (Week 12), the LY3002813 dose will not be escalated.

Table AACG.7.1 shows the 2 treatment regimens during the double-blind period.

The study also includes the use of the diagnostics flortaucipir F18 PET (for the determination of paired helical filament deposits of tau [tau PHF deposits]) and florbetapir F18 PET (for the determination of brain amyloid plaque deposits). Information regarding the use of these diagnostics in the study is provided in Appendix 5 and Appendix 6, respectively.

Table AACG.7.1. Treatment Regimens, Double-Blind Period

Regimen	Dose Visit 2 (Week 0) through Visit 21 (Week 76)
LY3002813	LY3002813 (700 mg intravenous infusion every 4 weeks x 3 doses, then 1400 mg intravenous infusion every 4 weeks for up to 72 weeks)
Placebo	Intravenously dosed placebo infusion every 4 weeks for up to 72 weeks

LY3002813 will be prepared by an unblinded pharmacist or other qualified unblinded personnel. LY3002813 will be administered by a blinded nurse or other qualified blinded personnel. The investigator or his/her designee is responsible for the following:

- explaining the correct use of the investigational agent(s) to the subject and/or legal representative
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection
- at the end of the study returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law

7.1.1. Packaging and Labelling

Clinical study materials will be labeled according to the country's regulatory requirements.

7.1.1.1. LY3002813 Packaging and Labelling

The drug product LY3002813 is supplied [redacted]. The drug product should be stored according to instructions on the label. [redacted]

Placebo is 0.9% (normal) saline.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be assigned a study (patient) number at Visit 1 and randomized to double-blind treatment at Visit 2. Patients will be randomized to LY3002813 or Placebo in a 1:1 ratio. For between-group comparability for site factor, patient randomization will be stratified by investigative site. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web response system (IWRS).

The IWRS will be used to assign a dosing regimen to each patient. Site personnel will confirm that they have located the correct packages by entering a confirmation number found on the label into the IWRS.

7.2.1. Selection and Timing of Doses

Assessment of LY3002813 safety and tolerability is a central objective; therefore, monitoring 100 patients on LY3002813 over 72 weeks provides data to assess safety for further clinical development.

The actual time of LY3002813 dose administration on the day of study visits will be recorded in the subject's case report form (CRF).

Note that at visits at which cognitive assessments are to be done, all cognitive scales are to be administered before IV study medication (LY3002813 or IV placebo) is administered.

7.2.1.1. LY3002813: Selection and Timing of Doses

The actual time of LY3002813 dose administrations on the day of study visits will be recorded in the subject's CRF. Intravenous study medication (i.e., IV placebo or LY3002813) is to be administered once every 4 weeks. Based on the permitted visit window (see Section 2), IV study medication could theoretically be administered at a 2-week interval. However, IV study medication must not be given at a dosing interval of less than 21 days at any time during the study. Intravenous study medication given at a dosing interval of less than 21 days at any time during the study will be considered a protocol deviation. The dose of LY3002813 was chosen based on PK/PD and safety from Studies AACC and AACD (see Section 5.5).

Infusions should occur over the course of a minimum of 30 minutes. If a patient demonstrates an infusion reaction to LY3002813, rescue medications may be administered at the discretion of the investigator (see Section 7.7). If indicated, the patient may be premedicated for subsequent infusions. See Section 9.4.7.1.1 or contact sponsor for further guidance. Patients should be observed for approximately 2 hours following each infusion of LY3002813 for the first 6 infusions. After the first 6 doses, a minimal post-infusion observation time of 60 minutes will be required for all subsequent infusions. However, patients who have had dosing restarted after ARIA-E are required to be monitored for 2 hours following infusion for a minimum of 3 subsequent infusions, and a minimum of 60 minutes postinfusion observation thereafter.

Sites must have resuscitation equipment available.

7.3. Blinding

This is a double-blind study, with design to maintain blinding to treatment. To preserve the blinding of the study, a minimal number of Lilly personnel will see the randomization table and treatment assignments before the study is complete. The independent external DMC will potentially be unblinded for safety evaluations and dose reduction decisions related to safety.

Emergency unblinding for AEs may be performed through the IWRS. This option may be used ONLY if the subject's well-being requires knowledge of the subject's treatment assignment. All unblinding events are recorded and reported by the IWRS.

If an investigator, site personnel performing assessments, or subject is unblinded, the subject must be discontinued from the study. In cases where there are ethical reasons to have the subject remain in the study, the investigator must obtain specific approval from a Lilly clinical research physician (CRP) for the subject to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted for medical management of the event. The patient's safety must always be the first consideration in making such a determination. If a patient's treatment assignment is unblinded, Lilly must be notified immediately. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

7.4. Dosage Modification

7.4.1. LY3002813 Dosage Modification for ARIA-E

LY3002813 dosage modifications will be done for the occurrence of ARIA-E in the following instances shown in Table AACG.7.2.

If a dosage reduction is required, then the LY3002813 dose will be reduced to the next lower dose (from 1400 mg to 700 mg or from 700 mg to placebo).

Table AACG.7.2. LY3002813 Dosage Modifications for First Occurrence of ARIA-E

ARIA-E SYMPTOMS	ARIA-E on MRI		
	Mild	**Moderate**	**Severe**
No symptoms	Continue on current dosing[a]	LY3002813 Dose reduction[a,b]	Temporary Discontinuation of LY3002813 (refer to Section 8.1.1.1)[b]
Mild	LY3002813 Dose reduction[a,b]	Temporary Discontinuation of LY3002813 (refer to Section 8.1.1.1)[b]	Temporary Discontinuation of LY3002813 (refer to Section 8.1.1.1)[b]
Moderate	Temporary Discontinuation of LY3002813 (refer to Section 8.1.1.1)[b]	Temporary Discontinuation of LY3002813 (refer to Section 8.1.1.1) [b]	Temporary Discontinuation of LY3002813 (refer to Section 8.1.1.1)[b]
Severe	Temporary Discontinuation of LY3002813 (refer to Section 8.1.1.1)[b]	Temporary Discontinuation of LY3002813 (refer to Section 8.1.1.1)[b]	Temporary Discontinuation of LY3002813 (refer to Section 8.1.1.1)[b]

[a] Investigator may choose to temporarily discontinue LY3002813 after discussion with the sponsor.

[b] If the patient has a second incidence of ARIA-E and has previously been dose reduced or temporarily discontinued from LY3002813, then LY3002813 will be permanently discontinued (see Section 8.1).

All Cases of ARIA-E will require unscheduled MRI scans every 4-6 weeks until ARIA-E has resolved. Further details are provided in the Operations Manual.

7.4.2. LY3002813 Dosage Modification for ARIA-H

There will be no dose reductions for changes in ARIA-H. Patients will be discontinued from dosing and IV administration if ARIA-H discontinuation rules are met (see Section 8.1). Patients will not be re-challenged with LY3002813 after dose discontinuation for ARIA-H.

All new cases of ARIA-H will require unscheduled MRI scans every 4-6 weeks until ARIA-H has stabilized without new findings.

7.5. Preparation/Handling/Storage/Accountability

The investigator or his/her designee is responsible for the following:

- confirming appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- ensuring that only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

- the investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation and final disposition records).

7.6. Treatment Compliance

The administration of all study medication should be recorded in the appropriate sections of the electronic case report form (eCRF).

7.6.1. LY3002813 Treatment Compliance

Because dosing occurs at study visits, patients who attend all visits and successfully receive LY3002813 infusions are automatically compliant with this treatment. Any infusion at which 75% (approximately 105 mL) or more of the infusion solution is given will be considered a complete infusion.

If a patient attends a visit but does not receive a complete infusion (e.g., due to technical complications), every effort should be made to complete the infusion within 24 hours if possible. If less than 75% of the infusion solution is given, this must be recorded as an incomplete infusion on the CRF.

Missed infusions should be recorded on the CRF.

7.7. Concomitant Therapy

All concomitant medication taken during the study must be recorded on the Concomitant Medication CRF. Patients and their study partners will be instructed to consult the investigator or other appropriate study personnel at the site before initiation of any new medications or supplements and before changing dose of any current concomitant medications or supplements.

To ensure standard of care for AD, use of approved treatments for AD is permitted in this study, and no medications are explicitly excluded from use. The section below provides additional guidance on managing concomitant medication use.

Allowed Medications. Use of approved or standard of care treatments for AD is permitted during the study, provided that such medications dose has been unchanged for 2 months before Visit 2. Doses of these medications should remain constant throughout the double-blind period (Visit 2 to Visit 21).

If a patient has recently stopped AChEIs and/or memantine, he or she must have discontinued treatment at least 2 months before Visit 2.

Other vitamins, medical food, or nutraceuticals given for their possible effects on AD may be continued on stable doses beginning 2 months before Visit 2.

Prior to V21, before a patient starts, stops, or changes doses of AChEIs and/or memantine or other treatments for their AD, the Sponsor or designee must be contacted to determine whether or not the patient should continue in the study and whether or not clinical outcome measures should be performed. Failure to notify Lilly or its designee regarding starting,

stopping or changing doses of AChEIs and/or memantine or other treatments for their AD prior to V21 will be considered a protocol deviation.

Nonmedication treatments for AD such as behavioral management are permitted but are subject to the same restrictions as medication treatment taken for AD.

Other concomitant medications that affect CNS function may be given if the dose remains unchanged throughout the study. Doses of these compounds should remain constant from 1 month before screening (Visit 1).

If unforeseen starting, stopping, or changing of stable doses of drugs affecting CNS function occurs prior to V21 of the study, Lilly or its designee must be contacted to determine whether or not the patient should continue in the study and whether or not outcome measures should be performed. ***Failure to notify Lilly or its designee regarding starting, stopping or changing doses of CNS medications prior to V21 of the study will be considered a protocol deviation***.

Use of benzodiazepines for treatment on an as-needed basis for insomnia or daily dosing as anxiolytics is permitted. Use of sedatives or hypnotics should be avoided for 8 hours before administration of the cognitive and functional tests unless they are given chronically.

If an infusion reaction occurs, rescue medications such as, but not limited to, diphenhydramine, epinephrine, and/or methylprednisolone may be administered at the discretion of the investigator. Administration of medications before an infusion to prevent a reaction does not cause a discontinuation of the patient from the study. If the need for concomitant medication arises, inclusion or continuation of the patient may be at the discretion of the investigator after consultation with a Lilly CRP. Concomitant therapy administered to treat an infusion reaction or as premedication for infusions should be documented.

Excluded Medications.

IgG therapy (also known as gamma globulin or intravenous immunoglobulin [IVIG]) is not allowed during the study.

7.8. Treatment after the End of the Study

7.8.1. Treatment after Study Completion

There is no planned open label extension at this time, or plan to otherwise make LY3002813 available to patients after conclusion of the study.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

Possible reasons leading to permanent discontinuation of study treatment:

- Subject Decision
    - the subject or the subject's designee; for example, legal guardian requests to discontinue investigational product.
- Discontinuation due to a hepatic event or liver test abnormality

  Subjects who are discontinued from investigational product due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via CRF/electronic data entry.

  Discontinuation of the investigational product for abnormal liver tests **should be considered** by the investigator when a subject meets one of the following conditions after consultation with the Lilly-designated medical monitor:

    - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8X upper limit of normal (ULN)
    - ALT or AST >5X ULN for more than 2 weeks
    - ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or international normalized ratio (INR) >1.5
    - ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
    - alkaline phosphatase (ALP) >3X ULN
    - ALP >2.5X ULN and TBL >2X ULN
    - ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

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

- Treatment with LY3002813 will be permanently discontinued in patients with:
    - a second incidence of ARIA-E after a previous dose reduction or temporary discontinuation of LY3002813
    - any increase in ARIA-H accompanied by clinically significant symptoms
    - >4 new microhemorrhages, >1 new area of superficial siderosis or significant worsening of pre-existing superficial siderosis, or any macrohemorrhage regardless of symptoms
    - an ARIA-E event reported as an SAE, regardless of severity of symptoms or MRI findings

- Treatment with LY3002813 will also be permanently discontinued in patients with:
    - Prolonged acute infusion reaction (i.e., not responsive to medication such as antihistamines, nonsteroidal anti-inflammatory drugs, and/or narcotics and/or brief interruption of infusion).
    - Adverse event or clinically significant laboratory value, ECG result, physical examination finding, MRI finding (such as symptomatic ischemic stroke), C-SSRS result, or vital sign measurement of such severity that, in the opinion of the investigator or Lilly-designated medical monitor, continued treatment is not in the best interest of the patient.
    - Severe non-compliance to the study protocol that results in a safety concern, in the judgment of the investigator.
    - The patient, for any reason, requires a treatment with an excluded therapeutic agent and temporary discontinuation criteria cannot be met (see Section 8.1.1.2).

Patients may permanently discontinue study treatment and remain in the trial. If LY3002813 infusion is permanently discontinued but the patient remains in the study, one PK sample should be collected at the soonest scheduled visit regardless if serum LY3002813 is on the Schedule of Activities at that visit. Dosing dates and times should be collected. Subsequent PK sample collection should follow the protocol Schedule of Activities for serum LY3002813 collection unless the scheduled visit exceeds 6 months since discontinuation of infusions. No additional serum collection for LY3002813 is required once the patient exceeds 6 months since discontinuation of LY3002813 infusions.

Subjects permanently discontinuing from the study prematurely for any reason should complete AE and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.1.1. Temporary Discontinuation from Study Treatment

8.1.1.1. Temporary Discontinuation from LY3002813 Study Treatment Due to ARIA-E

Temporary discontinuation from LY3002813 treatment is allowed for ARIA-E if the ARIA-E meets the temporary discontinuation criteria shown in Table AACG.7.2.

In cases of ARIA-E where the protocol indicates continued dosing or a dose reduction rather than temporary discontinuation (see Table AACG.7.2), the investigator may choose to temporarily discontinue LY3002813 after discussion with the sponsor. This will require choosing not to dispense LY3002813 through IWRS at relevant visits.

Study drug (LY3002813) may be restarted following a first incidence of ARIA-E at the discretion of the investigator if dosing is temporarily discontinued due to ARIA-E and there is complete resolution of symptoms and radiologic findings within 16 weeks after the temporary drug discontinuation.

If ARIA-E symptoms and radiologic findings have not completely resolved within 16 weeks, then the patient will be permanently discontinued from LY3002813 treatment.

Study drug may be restarted at either 700 mg or placebo, double blinded, depending on the original study arm to which the patient is randomized.

An unscheduled safety MRI scan will be required 4-6 weeks after dose restarts.

8.1.1.2. Temporary Discontinuation from LY3002813 Study Treatment for Reasons Other than ARIA-E

Temporary discontinuation from LY3002813 treatment is allowed if a short-term treatment of an excluded medication is necessary, secondary to hospitalization, personal circumstances or to evaluate the study drug impact on an uncertain AE. Study drug may be restarted at the investigator's discretion. If temporary discontinuation is due to an AE, it should be reported to the Lilly CRP. Temporary treatment discontinuation and re-starting should be documented. Restarting treatment after a discontinuation period that is greater than 12 weeks should be discussed between the investigator and Lilly CRP.

8.1.2. Discontinuation of Inadvertently Enrolled Subjects

If the sponsor or investigator identify a subject who did not meet enrollment criteria and was inadvertently enrolled, then the subject should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the subject to continue on study treatment. If the investigator and the sponsor CRP/CRS agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP/CRS to allow the inadvertently enrolled subject to continue in the study with or without treatment with investigational product.

Safety follow-up is as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events) and Section 9.4 (Safety) of this protocol.

8.2. Discontinuation from the Study

Patients who do not meet entry criteria or who are excluded by exclusion criteria from Visit 1 tests and procedures should be discontinued from the study before randomization as an entry failure.

Patients who exhibit any of the following conditions during the study that may possibly be related to study drug will be discontinued from the study, but will be encouraged to undergo final assessment visits and procedures as outlined in the Schedule of Activities (Section 2):

- Patients who require a ferromagnetic implant or insertion of a cardiac pacemaker that is not MRI-compatible will be discontinued from study drug and from the study; and, with the exception of an MRI, should have end-of-therapy and/or end-of-study procedures performed as shown in the Schedule of Activities (Section 2).

Subjects will also be discontinued from the study in the following circumstances:

- enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged by sponsor not to be scientifically or medically compatible with this study

- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- investigator decision
    - the investigator decides that the subject should be discontinued from the study
    - if the subject, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- subject decision
    - the subject or the subject's legal representative requests to be withdrawn from the study

Subjects discontinuing from the study prematurely for any reason must complete AE and other safety follow-up per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol. In addition, subjects discontinuing from the study prematurely should be encouraged to return to the site beginning 12 weeks after their ED visit for immunogenicity and safety assessments (Visits 801 through 804, as described in Section 5.1.3).

8.3. Lost to Follow-Up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact subjects who fail to return for a scheduled visit or who were otherwise unable to be followed up by the site.

Site personnel, or an independent third party, will attempt to collect the vital status of the subject within legal and ethical boundaries for all subjects randomized, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined, this will be documented and the subject will not be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect vital status information.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing).

Appendix 2 lists the clinical laboratory tests that will be performed for this study.

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

Screening measures used for diagnosis and establishment of study eligibility are described elsewhere (Section 5.1.1.1).

Cognitive and functional testing will be administered using an eCOA tablet. The audio voice recordings of the rater's questions and the patient's and study partner's responses will also be collected via the eCOA tablet during administration of the cognitive and functional testing for central monitoring of rater scale administration (Appendix 3, 3.2.1). Cognitive and functional testing for each patient should be performed at approximately the same time on each day that testing occurs to reduce potential variability. Note that the ADAS-Cog and MMSE must be administered by a different rater than the ADCS-ADL and CDR. These 2 raters should continue doing the same scale with the same patient throughout the study. If possible, each assessment should be performed on a given patient by the same rater at each visit. The principal investigator (PI) has the responsibility of selecting the raters who will administer the instruments at the site, as long as all training requirements have been met by those raters (Appendix 3, 3.1.5).

When administered, cognitive and functional testing should be performed first, before medical procedures that could be stressful for the patient (e.g., blood draws). Note that some procedures (MRI, flortaucipir F18 PET tau imaging, florbetapir F18 PET amyloid imaging) can be conducted on other days within the visit window.

9.1.1. Primary Efficacy Assessments

Integrated Alzheimer's Disease Rating Scale (iADRS; Wessels et al. 2015). The iADRS represents a composite that was developed using both a theory-driven approach (incorporating measures of both cognition and function) and a data-mining approach (identifying the most sensitive combination of scales through analysis of data from the Alzheimer's Disease Neuroimaging Initiative and the LY2062430 EXPEDITION, EXPEDITION2, and EXPEDITION3 studies). The iADRS is a simple linear combination of scores from 2 well-established, therapeutically sensitive, widely accepted measures in AD, the ADAS-Cog_{13} and the ADCS-iADL, measuring the core domains of AD. All items of these 2 scales are included without additional weighting of items, yielding face validity and ease of interpretation of the composite relative to its components.

The iADRS score will be derived from the ADAS-Cog$_{13}$ and the ADCS-iADL and will be the primary efficacy measure. The ADAS-Cog$_{13}$ and the ADCS-ADL will be the actual scales administered to patients.

9.1.2. Secondary Efficacy Assessments

Additional clinical outcome measures should be administered in the same order at every visit, immediately following assessment of the ADAS-Cog$_{13}$. To minimize missing data, the rater should include each measure orally with the patient or study partner (as designated in instructions), recording responses appropriately. The same study partner should be used as the informant at all visits.

9.1.2.1. Alzheimer's Disease Assessment Scale—Cognitive subscale (ADAS-Cog$_{13}$)

The ADAS-Cog$_{13}$ is a rater-administered instrument that was designed to assess the severity of the dysfunction in the cognitive and noncognitive behaviors characteristic of persons with AD (Rosen et al. 1984). The ADAS-Cog$_{13}$ should be administered by the same rater from visit to visit to reduce potential variability. The cognitive subscale of the ADAS, the ADAS-Cog$_{13}$, consists of 13 items assessing areas of cognitive function most typically impaired in AD: orientation, verbal memory, language, praxis, delayed free recall, digit cancellation, and maze-completion measures (Mohs et al. 1997). The ADAS-Cog$_{13}$ allows better discrimination of differences among mild patients than the ADAS-Cog$_{11}$, which will be included as a secondary outcome. The ADAS-Cog$_{13}$ scale ranges from 0 to 85, with higher scores indicating greater disease severity.

9.1.2.2. Alzheimer's Disease Cooperative Study—Activities of Daily Living Inventory (ADCS-ADL)

The ADCS-ADL is a 23-item inventory developed as a rater-administered questionnaire that is to be answered by the patient's study partner (Galasko et al. 1997, 2004). The ADCS-ADL should be administered by the same rater from visit to visit to reduce potential variability. The ADCS-ADL subset of items (items 7 to 23) for instrumental activities of daily living (ADCS-iADL) will be used as a secondary efficacy measure. The focus in the early symptomatic AD population is on the instrumental activities of daily living (iADLs) rather than the basic activities of daily living (bADLs), which are thought to be affected in more severe stages of the disease. The range for the iADL score is 0 to 56, with lower scores indicating greater disease severity. For each of the specific items, the study partner is first asked if the patient attempted the ADL during the past 4 weeks. If the patient did attempt the ADL, the study partner is asked to rate the patient's performance level based on a set of performance descriptions. Scores for each item and the overall score for the tool are calculated. The range for the total ADCS-ADL score is 0 to 78, with higher scores indicating greater level of impairment. Separate scores for the bADLs (0 to 22) will also be computed.

9.1.2.3. Clinical Dementia Rating Scale (CDR-SB)

The CDR is a semi-structured interview performed with the patient and study partner (informant) that provides an index of global functioning (Berg e al. 1992). The CDR should be administered by the same rater from visit to visit to reduce potential variability. The informant is queried about the patient's memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The patient's memory, orientation, judgment, and problem-solving ability are assessed. Higher scores indicate greater disease severity. By assigning a severity score for each of the 6 domains, a total score known as sum of boxes is obtained—hence the abbreviation, CDR-SB.

9.1.2.4. Mini-Mental State Examination (MMSE)

The MMSE is a brief instrument used to assess cognitive function in patients (Folstein et al. 1975). The MMSE should be administered by the same rater from visit to visit to reduce potential variability. The instrument is divided into 2 sections. The first section measures orientation, memory, and attention. The maximum score for the first section is 21. The second section tests the ability of the patient to name objects, follow verbal and written commands, write a sentence, and copy figures. The maximum score for the second section is 9. The range for the total MMSE score is 0 to 30, with lower scores indicating great level of impairment.

9.1.3. Biomarker Efficacy Measures (Double-Blind Period)

Florbetapir F18 PET scan. Change in amyloid burden (as assessed by florbetapir F18 PET signal) will be compared in LY3002813- and placebo-treated patients for those patients who undergo florbetapir F18 PET scans at baseline, Week 52 [Visit 15], and Week 76 [Visit 21] or ED) as described in the Schedule of Activities (Section 2).

Flortaucipir F18 PET scan. Change in tau burden (as assessed by flortaucipir F18 PET signal) will be compared in LY3002813- and placebo-treated patients for those patients who undergo both baseline and endpoint (Visit 21 [Week 76] or ED) flortaucipir F18 scans as described in the Schedule of Activities (Section 2).

Volumetric MRI. Magnetic resonance imaging of the brain will be performed according to the Schedule of Activities (Section 2). LY3002813- and placebo-treatment effects on volumetric MRI will be assessed and compared to evaluate the loss of brain volume that occurs in AD patients.

9.1.4. Appropriateness of Efficacy Assessments

The iADRS, the primary efficacy measure, is a simple linear combination of scores from 2 well-established, therapeutically sensitive, widely accepted measures in AD, the ADAS-Cog_{13} and the ADCS-iADL, measuring the core domains of AD. It represents a composite that was developed using both a theory-driven approach (incorporating measures of both cognition and function) and a data-mining approach (identifying the most sensitive combination of scales through analysis of data from the Alzheimer's Disease Neuroimaging Initiative and the LY2062430 EXPEDITION, EXPEDITION2, and EXPEDITION3 studies). Composite endpoints have been increasingly used as primary endpoints in clinical trials (Freemantle et al.

2003). Liu-Seifert et al. (2017) demonstrated that the treatment effect size of the iADRS composite is greater than the minimum treatment effect size of its components and that above certain thresholds of correlations of components and ratios of component effect sizes, the composite may outperform its components.

The secondary efficacy measures described in Section 9.1.2 are established measures of cognitive and functional outcomes, as well as behavioral symptoms associated with AD dementia, and considered appropriate assessments for the early symptomatic AD population.

In addition, the primary target engagement outcome is the reduction of cerebral amyloid as measured by quantitative amyloid PET imaging (florbetapir F18_PET SUVr) assessed at baseline, 24 weeks, 52 weeks and at 76 weeks after starting treatment. The postbaseline amyloid PET scans are aimed to assess the time course of amyloid reduction and sustainability of amyloid reduction. Reduction of paired helical filaments of cortical tau will be quantitatively assessed by tau PET imaging at baseline and 76 weeks.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient to discontinue the investigational product before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the informed consent form (ICF) is signed, study site personnel will record via CRF/electronic data entry the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure, investigational product, including radiopharmaceutical tracers, via CRF/electronic data entry.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, study device and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a patient's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via CRF/electronic data entry, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (i.e., immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs occurring after signing the ICF are recorded in the CRF/electronic data entry and assessed for serious criteria. The SAE reporting to the sponsor begins after the patient has signed the ICF and has received investigational product, including radiopharmaceutical tracers. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Section 9.2) if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Patients with a serious hepatic AE should have additional data collected using the CRF/electronic data entry.

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the patient disposition CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.1.2. Adverse Events of Special Interest

Specific safety topics of interest for this study include, but are not limited to, the following:

- ARIA-E
- ARIA-H
- Hypersensitivity (immediate and non-immediate), including infusion-related reactions
- Peripheral nervous system, central nervous system and muscle effects

The topics listed above, as well as other topics which may be subsequently determined by the sponsor, will be subject to enhanced surveillance activities. Additionally, the topics above will be analyzed for presentation in the Clinical Study Report in accordance with the Statistical Analysis Plan.

9.2.2. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

9.3. Treatment of Overdose

There is no known antidote to LY3002813. In case of overdose, use appropriate monitoring and supportive therapy.

9.4. Safety

9.4.1. Physical and Neurological Examinations

Complete physical examinations will be performed at screening, baseline, and Weeks 12, 24, 52, 76, and ED as indicated in the Schedule of Activities (Section 2). Brief physical examinations will be performed at Weeks 36 and 64. The complete physical examination will include assessment of the following: general appearance; skin, head and neck; lymph nodes; thyroid; abdomen (bowel sounds, liver and spleen palpation); back (costovertebral angle tenderness); and musculoskeletal, cardiovascular, and respiratory systems. The brief physical examination will include assessments of the skin, lungs, cardiovascular system, and abdomen (bowel sounds, liver and spleen palpation).

Complete neurological examinations will be performed as indicated in the Schedule of Activities (Section 2). The examinations will include a thorough assessment of gait, balance, coordination, cranial nerves, sensory and motor systems, and reflexes. If necessary given the training of the principal investigator, a neurologist will be consulted in the event of significant new findings.

If a clinically meaningful change in an MRI is noted during the study, an additional full neurological exam will be performed as soon as possible, along with any other medical follow-up deemed necessary by the investigator.

9.4.2. Electrocardiograms

For each patient, 12-lead digital ECGs will be collected as triplicates during the double-blind period according to the Schedule of Activities (Section 2). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Consecutive replicate ECGs will be obtained at approximately 1-minute intervals. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs (more replicates) than expected at a particular time point is allowed when needed to ensure high-quality records.

Electrocardiograms will initially be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the subject meets entry criteria at the relevant visit(s) and for immediate patient management, should any clinically relevant findings be identified.

After enrollment, if a clinically significant increase in the QT/corrected QT (QTc) interval from baseline or other clinically significant quantitative or qualitative change from baseline is identified, the patient will be assessed by the investigator for symptoms (e.g., palpitations, near syncope, syncope) and to determine whether the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed. The investigator or qualified designee must document his/her review of

the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point.

All digital ECGs will be electronically transmitted to a designated central ECG laboratory. A cardiologist at the central ECG laboratory will then conduct a full overread on 1 of the replicates (including all intervals). A report based on data from this overread will be issued to the investigative site. For each set of replicates, the cardiologist will determine the RR and QT intervals, and heart rate on the ECGs that were not fully overread. These data are not routinely reported back to the investigative site. All data from the overreads will be placed in the Lilly database for analytical and study report purposes.

When there are differences in ECG interpretation between the investigator (or qualified designee) and the cardiologist at the central ECG laboratory, the investigator's (or qualified designee's) interpretation will be used for study entry and immediate patient management. Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report writing purposes.

The investigator (or qualified designee) must document his/her review of 1 of the replicate ECGs printed at the time of collection, the final overread ECG report issued by the central ECG laboratory, and any alert reports.

9.4.3. Vital Signs

Vital signs, including temperature, will be measured at all visits.

9.4.3.1. Blood Pressure

Sitting blood pressure and pulse will be measured after 5 minutes in the sitting position at **all** visits. In addition, orthostatic blood pressure and pulse will be measured supine and standing at designated visits, as detailed in the Schedule of Activities (Section 2).

Orthostatic Blood Pressure Monitoring: For orthostatic blood pressure monitoring, subjects should be supine for at least 5 minutes and stand for at least 3 minutes prior to taking the respective measurements. If the subject feels unable to stand, only supine vital signs will be recorded.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms.

Any clinically significant findings from vital signs measurement that result in a diagnosis and that occur after the patient receives the first dose of study treatment should be reported to Lilly or its designee as an AE via CRF/electronic data entry.

9.4.3.2. Height, Weight, and Body Temperature

Height and body weight will be measured. Measurements should be taken without shoes and, when possible, the same scale should be used for all measurements. Body mass index (BMI) will be calculated from the height and body weight. Temperature will be recorded using an oral or tympanic (or other acceptable route) thermometer.

Body weight will be collected on the laboratory requisition for creatinine clearance calculations. Any body weight data entered into the eCRF will be used for the overall data analysis.

9.4.4. Laboratory Tests

For each patient, laboratory tests detailed in (Appendix 2) should be conducted according to the Schedule of Activities (Section 2).

With the exception of laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of investigational product should be reported to Lilly or its designee as an AE via CRF/electronic data entry.

9.4.5. Immunogenicity Assessments

Where local regulations and ERBs allow, at the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 10 mL each will be collected to determine antibody production against LY3002813. To interpret the results of immunogenicity, a venous blood sample will be collected, if warranted, at the same time points to determine the serum concentrations of LY3002813. All samples for immunogenicity should be taken predose when applicable and possible.

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of LY3002813 at a laboratory approved by the sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of LY3002813. The testing paradigm is outlined in Section 10.3.4.6.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and ERBs allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to LY3002813. Any samples remaining after 15 years will be destroyed.

9.4.6. Other Tests

9.4.6.1. Columbia Suicide Severity Rating Scale – Adult Version

Consistent with Food and Drug Administration (FDA) regulatory guidance (FDA 2012), any occurrence of suicide-related thoughts and behaviors will be assessed as indicated in the Schedule of Activities (Section 2). The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the corresponding assessment period. The scale includes suggested questions to elicit the type of information needed to determine if a suicide-related thought or behavior occurred.

The first time the scale is administered in this study, the C-SSRS “Baseline” version will be used, and the findings will constitute the baseline assessment. The C-SSRS “Since Last Visit” scale will be used for all subsequent assessments.

The C-SSRS will be administered to the patient with the study partner/study informant present or available by telephone, after the cognitive and functional assessments. Responses from both the study partner/study informant and patient will be considered when administering the scale. If a suicide-related thought or behavior is identified at any time during the study, a thorough evaluation will be performed by a study physician, and appropriate medical care will be provided.

The Lilly Self-Harm Supplement should be completed every time the C-SSRS is administered. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, then the Lilly Self-Harm Follow-Up form will be used to collect additional information to allow for a more complete assessment of these behaviors.

9.4.6.2. Magnetic Resonance Imaging

Magnetic resonance imaging of the brain will be performed according to the Schedule of Activities (Section 2) and as clinically indicated. This technology will be used to check for evidence of ARIA-H or ARIA-E, and other clinically relevant inclusion/exclusion and safety findings (The MRI data will also be used to calculate brain volumes, as noted in Section 9.1.3).

The MRI scans will be reviewed by the investigator or qualified designee for immediate patient management. Any clinically significant findings noted at baseline that result in a diagnosis should be recorded as a preexisting condition or AE. After the MRI scan is read locally, the MRI scans will be sent for analysis to a centralized MRI vendor designated by Lilly. Final MRI eligibility at screening will be determined by the centralized MRI vendor designated by Lilly and the MRI results will be reported to the site as “does” or “does not” meet MRI eligibility criteria. Specific analyses of the scans including assessments of ARIA-H and ARIA-E and calculations of brain volumes will be interpreted by the centralized MRI vendor for data analysis and report-writing purposes. Results of centrally read MRIs regarding patient care/safety will be reported back to sites.

9.4.6.3. Ophthalmological Examination

While the BACE inhibitor LY3202626 is no longer being administered in this study (see Section 5.1), ophthalmological examinations in patients who previously received LY3202626 or oral placebo will be performed at the next scheduled examination time point after their final dose of oral study medication (see the Schedule of Activities [Section 2]). Patients who received LY3202626/oral placebo after their Visit 9 ophthalmological examination are to have an unscheduled ophthalmological examination at the next available opportunity. Patients screened or randomized under the current amendment are not required to undergo any ophthalmological examinations at baseline or any other study visits.

Patients who previously received LY3202626 or oral placebo will undergo comprehensive ophthalmological examinations performed by an ophthalmologist or optometrist (where permitted by law) to assess visual function and morphology. Scheduled examinations will include the following: visual acuity, intraocular pressure, dilated funduscopic exam (dilation only performed in patients without contraindication to mydriatics), slit lamp exam, color photography of the retina, and optical coherence tomography (OCT) or equivalent; examinations

will also include color vision assessment. Assessments will preferably be performed by the same ophthalmologist or optometrist for each patient's visit. Patients who complain of vision disturbance, such as change in field of vision, color, acuity or anything potentially localizable to the retina, during the clinical trial should be referred to the ophthalmologist or optometrist (where permitted by law) for unscheduled evaluation.

Data from the ophthalmological examination visits will be provided from the local ophthalmologist or optometrist to the investigator.

The local ophthalmologist or optometrist will review the color photography and OCT to aid in immediate patient management. Additionally, the color photography of retina and OCT will be analyzed by a central reader.

Unblinded results of the eye safety data will be reviewed by the DMC.

Any clinically significant findings that result in a diagnosis should be reported to Lilly or its designee as a pre-existing condition or AE via eCRF per Section 9.2. The PI will make all final determinations of AEs in consultation with performing eye examiner, if applicable.

9.4.6.4. Dermatological Examination

While the BACE inhibitor LY3202626 is no longer being administered in this study, complete dermatological examinations in patients who previously received LY3202626 or oral placebo will be performed at the next scheduled examination time point after their final dose of oral study medication (see the Schedule of Activities [Section 2]). Patients who received LY3202626/oral placebo after their Visit 8 dermatological examination are to have an unscheduled dermatological examination at the next available opportunity. Patients screened or randomized under the current amendment are not required to undergo any skin exams at baseline or any other study visits.

This examination will preferably be performed by the same dermatologist for each patient's visit. All dermatological examinations must be performed by a dermatologist who will inspect the patient's unclothed full body using an ultraviolet (UV) light. The initial examination will include Fitzpatrick skin-type classification scale.

At each examination, abnormal hypopigmentation will be assessed by location, percentage of body surface area involvement, degree (partial/decreased pigmentation to complete depigmentation), and other findings in or around the hypopigmented area (such as redness or induration). A static physician's global assessment (sPGA) will be used to determine the patient's overall hypopigmentation severity at a given time point using a visual analog scale (VAS) ranging from 0 to 100. In addition, patients noted to have evidence of hypopigmentation will be asked to record how bothersome they find the hypopigmentation on a VAS ranging from 0 to 100. Skin photographs may be taken as appropriate for generating supporting documentation, but not for the purpose of primary clinical dermatologic evaluation or for data generation or analysis. A punch biopsy may be obtained at the discretion of the dermatologist.

Unblinded results of the dermatological safety data will be reviewed by the DMC.

Any clinically significant findings that result in a diagnosis should be reported to Lilly or its designee as a pre-existing condition or AE via eCRF per Section 9.2. The PI will make all final determinations of AEs in consultation with the dermatologist.

9.4.7. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the data monitoring board (an advisory group for this study formed to protect the integrity of data; refer to Interim Analyses section [Section 10.3.6]) can conduct additional analyses of the safety data.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly clinical research physician or scientist will, as appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist, and periodically review:

- trends in safety data
- laboratory analytes including blood hematology, chemistry, and urinalysis
- AEs including monitoring of hypersensitivity and infusion reactions, AEs associated with anti-LY3002813 antibodies (immunogenicity), ARIA-H, ARIA-E, ECG findings, neurological findings, hemorrhagic stroke, microhemorrhage (cerebral microhemorrhage, cerebellar microhemorrhage, brain stem microhemorrhage) as identified by investigator, and suicide-related thoughts and behaviors.

9.4.7.1. LY3002813 Hypersensitivity (Immediate and Non-immediate), Including Infusion-Related Reactions

9.4.7.1.1. Premedication for Infusions

Premedication for dosing is not planned. However, if an infusion reaction occurs, appropriate medication may be used as determined by the study investigators (see Section 7.7). The patient may be premedicated for subsequent infusions. If infusion reactions are observed, but review of the data suggests that dosing may continue, administration of medicines such as acetaminophen (500 to 1000 mg) and/or an antihistamine, and/or methylprednisolone (or other corticosteroid) may be administered before starting subsequent infusions at the discretion of the investigator. Any premedication given will be documented as a concomitant therapy (see Section 7.7).

9.4.7.1.2. Management of Infusion Reactions

There is a risk of an infusion reaction with any biological agent; therefore, all patients should be monitored closely. Symptoms and signs that may occur as part of an infusion reaction include, but are not limited to, fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash, pruritus, myalgia, and dizziness. In the event that an infusion reaction occurs, the following guidance should be followed:

- the investigational product infusion should be slowed or stopped, depending on the symptoms/signs present
- if slowed, the infusion should be completed at the slower rate, as tolerated and documented in the CRF
- if stopped, no further attempts to administer the investigational product will be made, and this will be documented in the CRF
- supportive care should be employed in accordance with the symptoms/signs.

Management of the infusion reaction should proceed according to the severity of the reaction as per the flowchart in the Manual of Operations. This may include, but is not limited to, rescue medications such as diphenhydramine, epinephrine, and/or methylprednisolone.

Additional data should also be collected via the CRF/electronic data entry. Please see the Operations Manual for more detail.

Additional, unscheduled stored serum samples for possible immune safety laboratory testing (including but not limited to β tryptase, total immunoglobulin E, and immune complex testing) should also be collected as close to the onset of the event as possible, but within 120 minutes, and 4-6 weeks after moderate or severe infusion reactions.

9.4.7.2. LY3002813 Immunogenicity

Patients are to return to the site for immunogenicity and safety follow-up visits (Visit 801 through Visit 804) beginning at Week 88 (or 12 weeks after their last dose of LY3002813) for collection of blood samples for anti-drug antibody (ADA; anti-LY3002813 antibody) and PK measurement, assessment of adverse events, C-SSRS, concomitant medications, and vital signs. The results of ADA testing remain blinded.

In order to preserve the blind, patients will need to complete Visits 801 through 804 until all patients in the trial have reached Visit 21 and datalock for the treatment period has been achieved. After **datalock**, the central laboratory will notify the sites and sponsor (or designee) as to whether a patient requires additional clinic visits beyond Visit 801, or meets criteria for discharge from immunogenicity follow-up. A patient will stop immunogenicity follow-up visits when he or she either completes 3 additional quarterly visits (e.g., Week 100, Week 112, and Week 124) or completes a visit at which his or her ADA returns to baseline (2-fold titer from baseline), whichever occurs first. Each subsequent visit after V801 will be scheduled only for those patients who meet the criteria for continued testing. Once the patient meets the criteria for discharge from follow-up, either a telephone contact or clinic visit should be conducted to complete the patient's participation in the study. See the Schedule of Activities (Section 2) for the timing of events and the measures to be assessed.

Treatment-emergent ADAs are defined in Section 10.3.4.6. A PK sample may be collected at the follow-up immunogenicity assessment(s) if warranted and agreed upon between both the investigator and sponsor.

In the event of drug hypersensitivity reactions (immediate or non-immediate), additional samples will be collected as close to the onset of the event as possible, but within 120 minutes, at the

resolution of the event, and 4-6 weeks following the event. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded. In the event of a finding of hypersensitivity, the investigator is to complete the CRF regarding the presence or absence of symptoms related to the hypersensitivity.

9.4.7.3. Hepatic Safety Monitoring

If a study patient experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, liver testing (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Hepatic Safety Data Collection

Additional safety data should be collected via the CRF/electronic data entry if 1 or more of the following conditions occur:

- elevation of serum ALT to ≥5X ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥ 2X ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2X ULN on 2 or more consecutive blood tests
- patient discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be a SAE

9.4.7.4. Amyloid-Related Imaging Abnormalities (ARIA-E and ARIA-H)

To ensure patient safety and to comply with regulatory guidance, the investigator is to consult with the Lilly-designated Medical Monitor regarding collection of specific recommended clinical information and follow-up MRIs. In the event of a finding of ARIA-E on MRI, the investigator is to complete the CRF regarding the presence or absence of symptoms related to the ARIA-E. While most cases of ARIA-E are asymptomatic, when symptoms do occur, they are reported to be most commonly headache, worsening of cognitive function, alteration of consciousness, seizures, unsteadiness, and vomiting. Even when symptomatic ARIA-E is present, in most cases, treatment is not required beyond a dose reduction (see Section 7.4.1) or temporary (see Section 8.1.1.1) or permanent (see Section 8.1) discontinuation of the LY3002813 treatment until the imaging abnormalities have resolved. If a patient simultaneously develops more than one of the symptoms suggestive of ARIA-E, then an unscheduled MRI should be performed. A single symptom suggestive of ARIA-E of sufficient severity may also warrant an MRI.

If the above-mentioned symptoms are reported, and ARIA-E is suspected, then the abnormality is best detected by fluid attenuation inversion recovery (FLAIR) sequences on MRI and ARIA-H is best detected with the T2* gradient-recalled echo on MRI.

An unscheduled MRI with these imaging sequences should be obtained upon suspicion of ARIA. If ARIA is present, it is recommended to repeat MRIs with these sequences every 4 to 6 weeks until resolution of ARIA-E or stabilization of ARIA-H is documented. For asymptomatic or mild symptoms, the patient can be observed; for moderate symptoms associated with ARIA-E, the use of oral or IV steroids can be considered. In the case of severe symptoms associated with ARIA-E, it is recommended to hospitalize the patient for close observation and consider the use of IV steroids such as high-dose dexamethasone or a similar agent.

The unscheduled MRI should be performed in the same manner as the currently scheduled MRIs in the protocol, which includes sending the images for central review.

9.4.8. Appropriateness of Safety Assessments

The clinical safety measurements (AE reporting, physical examinations, neurological examinations, vital signs, ECGs, and clinical safety laboratory tests [including immunogenicity]; Section 9.2 and Section 9.4) are well-established methods in drug development research and are standard procedures for clinical trials.

Performance of MRIs is indicated based on the potential for the occurrence of ARIA during treatment with LY3002813. Therefore, Study AACG will include serial MRIs beginning at baseline and following dosing according to the Schedule of Activities for assessment of ARIA.

LY3002813 is an antibody therapy. As noted previously, a high prevalence of LY3002813 ADAs was observed in Study AACC and AACD; therefore, immunogenicity analyses are indicated. Blood samples for the assessment of immunogenicity will be taken at regular intervals throughout the dosing and follow-up periods.

Performance of ophthalmological and dermatological examinations is indicated in subjects who were previously treated with LY3202626, based on the potential for the occurrence of adverse retinal effects and hypopigmentation, respectively, during treatment with LY3202626. While LY3202626 is no longer being administered in this study, dermatological and ophthalmological examinations in subjects who previously received this therapy or oral placebo will be performed at the next scheduled examination time point after their final dose of oral study medication, in accordance with the Schedule of Activities (Section 2). Patients who received LY3202626/oral placebo after their Visit 8 or 9 dermatological or ophthalmological examination are to have an unscheduled examination at the next available opportunity. Patients screened or randomized under the current amendment are not required to undergo any dermatological or ophthalmological examinations at baseline or any other study visits.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 4 mL each will be collected to determine the serum concentrations of

LY3002813. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

A maximum of 3 blood samples per patient may be drawn at additional time points during the study, if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor.

If LY3002813 infusion is permanently discontinued but the patient remains in the study, one PK sample should be collected at the soonest scheduled visit regardless if serum LY3002813 is on the Schedule of Activities at that visit. Dosing dates and times should be collected. Subsequent PK sample collection should follow the protocol Schedule of Activities for serum LY3002813 collection unless the scheduled visit exceeds 6 months since discontinuation of infusions. No additional serum collection for LY3002813 is required once the patient exceeds 6 months since discontinuation of LY3002813 infusions.

Bioanalytical samples collected to measure LY3002813 or LY3202626 concentrations will be retained for a maximum of 1 year following last subject visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism, protein binding, or bioanalytical method development/validation work.

9.6. Pharmacodynamics

9.6.1. Clearance of Amyloid Deposits

Florbetapir F18 PET provides quantitative assessment of amyloid plaque deposition in the brain and can serve as a PD biomarker of clearance of amyloid deposits.

Clearance of amyloid deposits (as assessed by florbetapir F18 PET signal) will be compared in LY3002813- and placebo-treated patients for those patients who undergo baseline, Visit 8 (Week 24), Visit 15 (Week 52) and endpoint Visit 21(Week 76) or ED florbetapir F18 PET scans as described in the Schedule of Activities (Section 2).

9.6.2. Accumulation of Tau Deposits

Flortaucipir F18 PET provides quantitative assessment of tau PHF in the brain and can serve as a PD biomarker of accumulation of tau deposits as AD progresses.

Extent of accumulation of tau PHF deposits (as assessed by flortaucipir F18 PET signal) will be compared in LY3002813- and placebo-treated patients for those patients who undergo baseline and endpoint Visit 21 (Week 76) or ED) flortaucipir F18 PET scans as described in the Schedule of Activities (Section 2).

9.7. Pharmacogenomics [OR] Genetics

9.7.1. Apolipoprotein E Genotyping

Apolipoprotein E (APOE) genotyping is a mandatory part of this study, unless country-specific laws and regulations prohibit this type of testing. Blood sampling for APOE genotyping will be performed as shown in the Schedule of Activities (Section 2). Neither patients nor investigators will receive the genotype results unless there is a country-specific law or regulation that requires notification of the results. Failure to collect samples for APOE will not be considered a protocol deviation if country-specific regulations prohibit the testing of genetic material or transportation of such material outside of the country.

9.7.2. Whole Blood Samples for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Section 2) where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to LY3002813 and to investigate genetic variants thought to play a role in AD. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel.

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs/investigational review boards (IRBs) impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3002813 and LY3202626 or after LY3002813 and LY3202626 become commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome wide association studies, and candidate gene studies. Regardless of technology utilized, genotyping data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including deoxyribonucleic acid (DNA), ribonucleic acid (RNA), proteins, lipids, and other cellular elements.

Serum, plasma, and whole blood RNA samples for biomarker research will be collected at the times specified in the Schedule of Activities (Section 2) where local regulations allow.

Samples will be used for research on the drug target, disease process, variable response to LY3002813 and/or LY3202626, pathways associated with AD, mechanism of action of LY3002813 and LY3202626, and/or research method or in validating diagnostic tools or assay(s) related to AD.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel.

Samples will be retained at a facility selected by Lilly or its designee for a maximum 15 years after the last patient visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3002813 and LY3202626 or after LY3002813 and LY3202626 become commercially available.

9.9. Medical Resource Utilization and Health Economics

Dependence, or the level of assistance required by a patient, has been suggested as a construct for assessing the effect of AD treatment. The process of increasing dependence on others is intended as a complementary measure to existing clinical measures in order to help explain the impact of AD on economic issues such as the risk of institutionalization and caregiver burden (McLaughlin et al. 2010; Spackman et al. 2013). Recently, the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL) scores were used to map individuals into one of six dependence levels (0 to 5): Level 0 – No iADL/bADL impairment; Level 1 – Some supervision needed on isolated iADLs; Level 2 – Supervision on multiple iADLs or loss of at least 1 household activity; Level 3 – Supervision on all types of iADLs or homebound; Level 4 – Supervision on some bADLs; and Level 5 – Impaired transfer or complete incontinence (Kahle-Wrobleski et al. 2015). An approach to transforming continuous functional scale scores into discrete levels of dependence was examined previously in a longitudinal observational study, with preliminary results suggesting acceptable validity and progression in dependence level over time (Kahle-Wrobleski et al. 2017). At baseline, 49.6% of those with mild AD dementia were dependence level 2 and 42.7% were at levels 3 or 4. At 18 months, the proportion of patients at level 2 declined to 31.2% while that at levels 3 and 4 rose to 58.8%. Analyses will be conducted to examine changes in dependence levels across the trial population as well as potential differences on dependence level by treatment group assignment.

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 250 subjects will be enrolled and randomized in a 1:1 ratio to the 2 treatment arms (placebo and LY3002813). It is expected that approximately 200 subjects will complete the double-blind treatment period of the study (approximately 100 per treatment arm). This sample size will provide approximately 84% power to demonstrate that the active treatment arm has a ≥ 0.6 posterior probability of slowing down iADRS progression over placebo by at least 3 points. The assumption for power calculation is that mean progression levels in the placebo and LY3002813 arms are approximately 12 and 6 points (50% slowing) over 18 months, respectively, with common standard deviation of 17. If the active treatment arm is placebo-like with no efficacy, the probability of passing the efficacy criterion specified above (i.e., false positive) is approximately 6%. The simulation for the power calculation and sample size determination was carried out in FACTS Version 6.0.

10.2. Populations for Analyses

For purposes of analysis, in general the following populations are defined unless otherwise specified:

For efficacy analysis, the Full Analysis Set will group patients according to randomized treatment assignment (LY3002813 or placebo), even if the patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. When change from baseline is assessed, patients will be included in the analysis only if both a baseline and at least 1 valid post-baseline measure are available.

For safety analysis, all patients who received at least 1 dose of randomized study treatment (LY3002813 or placebo) will be included in the safety analysis set. In safety data presentations, erroneously treated patients (e.g., those randomized to “Treatment A” but actually given “Treatment B”) will be accounted for in their actual treatment groups.

There were approximately 48 patients randomized before the removal of LY3202626 treatment in protocol amendment (d) (about 16 each in the LY3002813 and LY3202626 combination therapy arm, LY3002813 monotherapy arm, and placebo arm). Patients already randomized to the former LY3002813 monotherapy arm and placebo arm will be pooled with patients randomized after protocol amendment (d) to form the Full Analysis Set and safety analysis set specified above. Data from patients randomized to the LY3002813 and LY3202626 combination therapy arm will be summarized separately and will not be included in treatment comparisons on efficacy and safety endpoints. The total number of patients to be randomized in the study is approximately 266.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Unless otherwise noted, all pairwise tests of treatment effects will be conducted at a 2-sided alpha level of 0.05; 2-sided CIs will be displayed with a 95% confidence level. All tests of interactions between treatment and other factors will be conducted at an alpha level of 0.05. Bretz' graphical approach may be utilized to provide strong control of the study wise Type I error rate for the primary and key secondary hypotheses at alpha level of 0.05 (Bretz et al. 2009; Bretz et al. 2011). Details on the graphical approach and testing strategy will be specified in the statistical analysis plan (SAP).

All efficacy analyses will follow the intent-to-treat (ITT) principle unless otherwise specified. An ITT analysis is an analysis of data by the groups to which subjects are assigned by random allocation, even if the subject does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol.

When change from baseline is assessed, subjects will be included in the analysis only if both a baseline and a postbaseline measure are available. Unless otherwise defined, a baseline measure is the last nonmissing observation collected prior to the first administration of study medications. Endpoint is the last nonmissing postbaseline measurement.

For MMRM models, observations collected at nonscheduled visits will not be included in the analyses.

A database lock is expected to occur after all randomized subjects have had chance to complete double-blind period of the study. Efficacy and safety analyses will be conducted based on data collected during double-blind period. Data collected during immunogenicity and safety follow-up period will be summarized and analyzed separately.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the SAP and clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

Details of the statistical methods are specified in the SAP for Study AACG.

10.3.1.1. Handling of Missing Items for Scales

If any of the individual items for ADAS-Cog or ADCS-ADL are missing or unknown, every effort will be made to obtain the score for the missing item or items.

For ADAS-Cog_{13}, if 4 or fewer of a total of 13 items are missing, the total score (maximum =85) will be imputed as follows: The total from remaining items will be multiplied by a factor that includes the maximum score for the missing items. For example, if the first item, "Word-Recall Task," which ranges from a score of 0 through 10 (maximum = 10), is missing, and the second item "Commands," which ranges from a score of 0 to 5 (maximum = 5), is missing, then the

multiplication factor = 85/(85 - [10 + 5]) = 85/70 = 1.21. Thus, the total score for this example will be the sum of the remaining 12 items multiplied by 1.21. The imputed number will be rounded up to the nearest integer. If more than 4 items are missing, the total score for ADAS-Cog$_{13}$ at that visit will be considered missing.

For the ADCS-iADL, if <30% of the items are missing, the total score will be imputed. The sum of the nonmissing items will be prorated to the sum of total items. The imputed number will be rounded up to the nearest integer. If the nearest integer is greater than the maximum possible score, the imputed score will be equal to the maximum score. If >30% of the items are missing, the total score for ADCS-iADL at that visit will be considered missing. The same imputation technique will be applied to the ADCS-ADL total score. Note that, depending on the specific item responses that are missing, it is possible to have an imputed total score for both the ADCS-iADL and the ADCS-ADL, an imputed total score for one but not the other, or both total scores missing.

The same imputation technique will be applied to the CDR-SB. If only 1 box (of 6) of the CDR is missing, the sum of the boxes will be imputed by prorating the sum from the other 5 boxes. If the score from more than 1 box is not available, the CDR-SB at that visit will be considered missing.

iADRS score is calculated as – ADAS-Cog$_{13}$ score + 85 + ADCS-iADL score. If either ADAS-Cog$_{13}$ or ADCS-iADL is missing, iADRS score will be considered missing.

For all other scales, if any item is missing, any total or sum involving that item will be considered missing.

10.3.2. Treatment Group Comparability

10.3.2.1. Subject Disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

The reasons for discontinuation will be collected when the patient's participation in the study ends and will be summarized by treatment group for all randomized subjects. The percentage of subjects discontinuing from each treatment group will be compared between groups using Fisher's exact test. The comparisons will be done for the overall percentage of patients who discontinue and for select specific reasons for discontinuation.

10.3.2.2. Subject Characteristics

The patient's age, gender, race, height, body weight, BMI (weight (kg) / [height (m)]^2), tobacco use, alcohol use, caffeine use, years of education, work status, time since onset of first AD symptoms, time since diagnosis, baseline MMSE, CBB score at Visit 1, apolipoprotein E (APOE) genotype (E4 carrier vs. non-carrier), having 1 or more first degree relatives with AD, and AChEI and/or memantine use at baseline will be recorded.

Baseline characteristics will be summarized by treatment group and overall. Summaries will include descriptive statistics for continuous and categorical measures. Fisher's exact test or Pearson's chi-square test will be used for treatment-group comparisons of categorical data. For continuous data, analysis of variance (ANOVA), with independent factors for treatment and investigator, will be used.

10.3.2.3. Prior and Concomitant Therapy

Prior medications are defined as those that stop before randomization (Visit 2). Concomitant medications are defined as those being taken on or after randomization (Visit 2). A summary of concomitant medications will be presented as frequencies and percentages for each treatment group. Fisher's exact test will be used to test for treatment differences between groups.

If the start or stop dates of therapies are missing or partial to the degree that determination cannot be made of whether the therapy is prior or concomitant, the therapy will be deemed concomitant.

Prior and concomitant medications will be listed.

Summary tables will also be provided for concomitant anticholinergics that affect cognitive function and AChEI/memantine medications.

Medications will be coded using the World Health Organization (WHO) drug dictionary.

10.3.2.4. Treatment Compliance

Summary statistics for LY3002813 treatment compliance will be provided for the total number of complete infusions received, duration of complete infusion, and volume of complete infusion by treatment group.

Frequencies and percentages of reasons why infusion was stopped will also be presented.

Summary statistics for LY3202626 treatment compliance will be provided for the proportion of patients who are compliant and noncompliant as noted in Section 7.6 of this protocol by treatment group.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary objective of this study is to test the hypothesis that IV infusion of LY3002813 will slow the cognitive and/or functional decline of AD as measured by the composite measure iADRS compared with placebo in patients with early symptomatic AD. This will be assessed using an MMRM analysis.

The change from baseline score on the iADRS at each scheduled postbaseline visit (according to the Schedule of Activities) during the treatment period will be the dependent variable. The model for the fixed effects will include the following terms: baseline score, pooled investigator, treatment, visit, treatment-by-visit interaction, baseline-by-visit interaction, concomitant AChEI and/or memantine use at baseline (yes/no), and age at baseline. Visit will be considered a categorical variable. The null hypothesis is that the contrast between the LY3002813 group versus placebo at the last visit equals zero. An unstructured covariance matrix will be used to

model the within-subject variance-covariance errors. If the unstructured covariance structure matrix results in a lack of convergence, the following tests will be used in sequence: heterogeneous Toeplitz covariance structure, heterogeneous autoregressive covariance structure, heterogeneous compound symmetry covariance structure, and compound symmetry covariance structure. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

The primary time point for treatment comparison will be at Week 76. The treatment group contrast in least-squares mean progression and its associated p-value and 95% CI will be calculated for the treatment comparison of LY3002813 vs. placebo using the MMRM model specified above. In addition, Bayesian posterior probability of the active treatment arm being superior to placebo by at least a margin of interest (25% slowing of placebo progression) will also be calculated assuming a non-informative prior.

10.3.3.2. Secondary Efficacy Analyses

Similar to the primary analysis, each of the secondary efficacy outcomes will be assessed using an MMRM analysis. These secondary efficacy outcomes include ADAS-Cog_{13}, ADCS-iADL, CDR-SB, and MMSE. For each secondary efficacy measure, the change from baseline score at each scheduled postbaseline visit (according to the Schedule of Activities) during the treatment period will be analyzed using the same MMRM model described for the primary analysis.

Longitudinal changes from baseline in amyloid plaque (as measured by florbetapir F18 PET scan) and vMRI parameters will be analyzed using MMRM including the following terms in the model: baseline biomarker value, treatment, visit, treatment-by-visit interaction, and baseline-by-visit interaction. The change from baseline to endpoint in tau SUVr (as measured by flortaucipir PET scan) will be analyzed using an analysis of covariance (ANCOVA) model with terms of baseline value and treatment.

Any additional analyses of secondary efficacy outcomes and biomarkers will be specified in the SAP.

10.3.4. Safety Analyses

All subjects who receive at least 1 dose of LY3002813 will be evaluated for safety and tolerability. Safety parameters (AEs, laboratory analytes, vital signs, ECGs, and MRIs) will be summarized using descriptive statistics for continuous variables and frequencies along with percentages for categorical variables during the treatment period.

10.3.4.1. Adverse Events

Treatment-emergent adverse events will be defined as events that first occurred or worsened on or after randomization (Visit 2). Should there be insufficient data for AE start date and stop date the AE will be considered treatment emergent.

Treatment-emergent adverse events will be calculated based on adverse event identifier (AEID) and coded according to established Medical Dictionary for Regulatory Activities (MedDRA) terms and summarized by MedDRA System Organ Class (SOC) and Preferred Term.

An overview of AEs, including the number and percentage of subjects who died, had SAEs, discontinued due to AEs, and who had treatment-emergent AEs (TEAEs), will be summarized by treatment group.

10.3.4.2. Vital Signs and Weight

Vital sign measurements and weight will be analyzed using continuous data (change from baseline) and categorical data (proportion of treatment-emergent abnormalities).

Summary statistics will be presented for observed values at baseline and for change from baseline results at each scheduled postbaseline visit and at endpoint(s). Systolic and diastolic blood pressure and pulse (collected in sitting position), temperature, and weight will be summarized.

The incidence of treatment-emergent abnormal high or low vital signs and weight will be summarized by treatment groups. Treatment-emergent vital sign evaluations are defined for evaluations collected after the initiation of study medication. Abnormal criteria for vital signs and weight are presented in Table AACG.10.1. Any vital sign or weight outside the criterion values will be considered abnormal.

Table AACG.10.1. Criteria for Abnormal Vital Signs

Vital Sign Parameter (Unit)	**Postbaseline Low Criteria**	**Postbaseline High Criteria**
Sitting Systolic Blood Pressure (mmHg)	Absolute value ≤90 and ≥20 decrease from baseline	Absolute value ≥160 and ≥20 increase from baseline
Sitting Diastolic Blood Pressure (mmHg)	Absolute value ≤50 and ≥10 decrease from baseline	Absolute value ≥100 and ≥10 increase from baseline
Sitting Pulse (bpm)	Absolute value <50 and ≥15 decrease from baseline	Absolute value >100 and ≥15 increase from baseline
Weight	≥4% decrease	≥4% increase
Vital Sign Parameter (Unit)	**Postbaseline Criteria for Abnormality**	
Orthostatic Systolic Blood Pressure (mmHg)	≥20 mmHg decrease in systolic blood pressure (supine to standing) (i.e., supine minus standing ≥20)	
Orthostatic Diastolic Blood Pressure (mmHg)	≥10 mmHg decrease in diastolic blood pressure (supine to standing) (i.e., supine minus standing ≥10 mm Hg)	
Orthostatic Pulse (bpm)	≥30 increase in bpm (standing to supine) (i.e., standing minus supine ≥30)	
Temperature	Absolute value ≥38.3°C and ≥1.1°C increase from baseline (Absolute value ≥101°F and ≥2°F increase from baseline)	

Abbreviation: bpm = beats per minute.

10.3.4.3. Laboratory Analyses

Laboratory measurements will be analyzed as continuous data (change from baseline) measured as International System Units (SI) or as categorical data (proportion of treatment-emergent abnormalities).

If there are multiple records of laboratory measurements at baseline or postbaseline visits, the last record will be used.

Change from baseline to postbaseline visits at which laboratory measurements are taken will be summarized using descriptive statistics.

For all laboratory analytes, frequencies of subjects with notable changes (i.e., increases or decreases of a prespecified amount unique to each analyte) from baseline to each postbaseline visit will also be summarized for all subjects and stratified by low, normal, or high at baseline.

10.3.4.4. Electrocardiograms

The ECG measurements will be analyzed using continuous data (change from baseline) and categorical data (proportion of treatment-emergent abnormalities).

Since ECG is measured in triplicates during the double-blind period, the average of triplicates will be used at baseline and each double-blind period visit. If there are multiple records after averaging ECG triplicates within a visit, the last record of averages will be used.

The analysis will be done for the following ECG measurements: heart rate, PR, QT, QTc, and RR intervals and QRS duration. All analyses of QTc will be carried out using the Fridericia correction (QTcF) method. These summaries will include data from each visit ECG measures are performed.

Change from baseline to each postbaseline visit at which ECG measurements are taken will be assessed using an MMRM model. The model for the fixed effects will include terms for the following independent effects: baseline ECG score, pooled investigator, treatment, visit, treatment-by-visit interaction, baseline-by-visit interaction and age at baseline. This analysis will be done separately for each ECG parameter.

Incidence of treatment-emergent abnormal ECGs will be assessed by comparisons at (1) anytime and (2) each postbaseline visit between treatment groups with Fisher's exact test. For analyses of treatment-emergent abnormal ECGs, baseline will be considered as all visits before the initiation of drug dose.

Abnormal ECG criteria are presented in Table AACG.10.2 and criteria for abnormal QTcF prolongation are presented in Table AACG.10.3.

Table AACG.10.2. Criteria for Abnormal ECG Parameters

ECG Parameter	Low Criteria	High Criteria
Heart Rate	<50 bpm	>100 bpm
PR Interval	<120 msec	≥220 msec
QRS Duration	<60 msec	≥120 msec
QTc Interval males females males and females	 <330 msec <340 msec	 ≥450 msec ≥470 msec > 500 msec

Abbreviations: bpm = beats per minute; ECG = electrocardiogram; QTc = corrected QT.

Table AACG.10.3. Criteria for Prolonged ECG QTcF Interval

QTc Delta Changes (msec)
>30
>60
>75

Abbreviations: QTc = corrected QT; QTcF = Fridericia-corrected QT.

Treatment-emergent high ECG parameters (heart rate, PR interval, QRS duration, and QT and QTcF intervals) are the values that are low or normal at all baseline visits and fall into the high abnormal categories in Table AACG.10.2 and Table AACG.10.3 postbaseline. Similarly, treatment-emergent low ECG parameters (heart rate, PR interval, and QRS duration) are the values that are high or normal at all baseline visits and fall into the low abnormal categories above.

For each treatment-emergent high ECG parameter in Table AACG.10.2, only subjects who were low or normal at baseline and have at least 1 postbaseline value will be included in the denominator when computing the proportion of subjects with treatment-emergent high values. Similarly, only subjects who were high or normal at baseline and have at least 1 postbaseline value will be included in the denominator when computing the proportion of subjects with treatment-emergent low values.

For prolonged QTcF interval assessments, when computing the proportion of subjects with treatment-emergent high abnormalities, only subjects who were normal at baseline and had a nonmissing result at that postbaseline visit will be included in the denominator. A treatment-emergent high value is defined as a change from normal value at all baseline assessments to a value greater than 450 msec for males and 470 msec for females at postbaseline.

In addition, treatment differences in the proportion of subjects who have normal baselines with a change to abnormal high or abnormal low values at any postbaseline visits will be summarized. Treatment-emergent qualitative ECG findings will also be summarized.

10.3.4.5. ARIA-E and ARIA-H

The incidence of ARIA-E will be summarized. Change in ARIA-E status from baseline, to each subsequent MRI (in the event of unscheduled MRIs), and to double-blind period endpoint (Visit 21) will be compared between treatment groups using Fisher's exact test.

The incidence of changes in ARIA-H will be summarized. Change in ARIA-H status from baseline to endpoint will be compared between treatment groups using Fisher's exact test. The number and percentage of subjects with increases in size of preexisting ARIA-H, number of subjects with increases in number of ARIA-H, and number of subjects with increases in size of preexisting and/or number of ARIA-H from baseline to endpoint will be summarized for both treatment groups and compared using Fisher's exact test.

Subjects with ARIA-E and subjects with ARIA-H that increased in size and/or number postbaseline, and subjects with any other MRI findings will be listed.

10.3.4.6. Evaluation of Immunogenicity

Subject samples will be analyzed using a 4-tiered approach. All samples will be assessed in Tier 1 (screening) for the possible presence of ADA. Samples found to produce a signal above or equal to the screening cut point will be assessed in Tier 2 to confirm specificity to LY3002813 (confirmation). Any samples confirmed as specific for anti-LY3002813 antibodies will be reported as "detected." All samples below the screening cut point (Tier 1) or not confirmed (Tier 2) will be reported as "not detected." Any "detected" sample in Tier 2 will be assessed in Tier 3 (titer assessment) and Tier 4 (neutralizing antibodies). Anti-drug antibodies titer values will be reported from Tier 3 titer assessment. Any samples above the Tier 4 assay cut point will be reported as "detected for neutralizing antibodies"; samples below the assay cut point in Tier 4 will be reported as "not detected for neutralizing antibodies."

The frequency and percentage of subjects with preexisting (baseline) ADA, ADA at any time after baseline, and TE ADA to LY3002813 will be tabulated. If no ADAs are detected at baseline, TE ADA are defined as those with a titer 2 fold (1 dilution) greater than the MRD of the assay. For samples with ADA detected at baseline TE ADA are defined as those with a 4-fold (2 dilutions) increase in titer compared to baseline. For the TE ADA subjects, the distribution of maximum titers will be described. The frequency of neutralizing antibodies may also be tabulated. The relationship between the presence of antibodies to LY3002813 and PK, PD, safety and/or efficacy assessment may be assessed.

10.3.4.7. Suicidal Ideation and Behavior

Suicide-related thoughts and behaviors, based on the C-SSRS, will be listed by subject and visit. Only subjects that show suicidal ideation/behavior will be displayed (i.e., if a subject's answers are all "no" for the C-SSRS, then that subject will not be displayed). However, if a subject reported any ideation or behavior at any time point, then all their ideation and behavior will be displayed, even if not positive.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Compartmental modeling of LY3002813 PK data using nonlinear mixed effects modeling or other appropriate software may be explored, and population estimates for clearance and central volume of distribution may be reported. Depending on the model selected, other PK parameters may also be reported. Exploratory graphical analyses of the effect of dose level or demographic factors on PK parameters may be conducted. If appropriate, data from other studies of LY3002813 may be used in this analysis.

Concentrations of LY3202626 were collected under the original version of this protocol, as well as amendments (a-c). These data will be summarized in the final study report and may be analyzed graphically. If appropriate, exploratory analyses may be conducted to evaluate potential relationships between LY3202626 concentrations and LY3002813 concentration.

The PK/PD relationships between plasma LY3002813 concentration and SUVr, cognitive endpoints, ARIA incidence rate or other markers of PD activity may be explored graphically. The relationship between the presence of antibodies to LY3002813 and PK, PD, safety and/or efficacy may be assessed graphically.

Additional modeling may be performed based on the results of the graphical analyses.

10.3.6. Interim Analyses

A limited number of pre-identified individuals may gain access to the limited unblinded data, as specified in the unblinding plan, prior to the interim or final database lock, in order to initiate the final population PK/PD model development processes for interim or final analyses. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded. It is intended that access prior to the final database lock will be granted after the last patient completes Visit 18 (after 64 weeks of treatment).

An independent external Data Monitoring Committee (DMC) is to monitor data on an ongoing basis to ensure the continuing safety of patients enrolled in this study. There will be periodic safety data reviews during the study and the external DMC is authorized to evaluate results from unblinded safety data reviews. The timing and operational details of the DMC safety data reviews are defined in DMC charter.

At least one interim analysis may be conducted for Study AACG; for example, when all randomized subjects have had a chance to complete 52 weeks of treatment (Visit 15) and data will be used to evaluate whether to stop the study for futility. Additional assessment of efficacy may also be evaluated at the interim analyses to inform future development of the compounds and platform. For such futility and efficacy analyses, an internal assessment committee (IAC), but external to the study team, is authorized to evaluate results from the unblinded interim analyses. Operational details and a quantitative framework to provide information for these decisions will be documented in the statistical analysis plan (SAP). Study sites will receive information about interim results ONLY if they need to know for the safety of their patients.

Unblinding details are specified in the unblinding plan section of the SAP or a separate unblinding plan document.

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
Aβ	amyloid β
AD	Alzheimer's disease
ADA	anti-drug antibodies
ADAS-COG$_{13}$	Alzheimer's Disease Assessment Scale – Cognitive subscale 13
ADCS-ADL	Alzheimer's Disease Cooperative Study—Activities of Daily Living Inventory
ADCS-bADL	Alzheimer's Disease Cooperative Study—basic activities of daily living
ADCS-iADL	Alzheimer's Disease Cooperative Study—instrumental activities of daily living
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
APOE	Apolipoprotein subtype E
ARIA-E	amyloid-related imaging abnormalities–edema/effusions (also known as vasogenic edema)
ARIA-H	amyloid-related imaging abnormalities–hemorrhage/hemosiderin deposition (also known as cerebral microhemorrhage)
AST	aspartate aminotransferase
BACE	β-site amyloid precursor protein cleaving enzyme
blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patients are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BMI	body mass index

bpm	beats per minute
CBB	CogState Brief Battery
CDR-SB	Clinical Dementia Rating Scale – Sum of Boxes
CIOMS	Council for International Organizations of Medical Sciences
Companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A	cytochrome P450 3A
DMC	data monitoring committee
ECG	electrocardiogram
eCOA	Electronic Clinical Outcome Assessment
ED	early discontinuation
ELISA	enzyme-linked immunosorbent assay
End of Study	End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last patient.
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
FAS	full analysis set
FDA	Food and Drug Administration
GCP	good clinical practice

HBsAg	hepatitis B surface antigen
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
IAC	internal assessment committee
iADRS	integrated Alzheimer's Disease Rating Scale (iADRS)
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (i.e., the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IVRS/IWRS	interactive voice-response system/interactive web-response system
MedDRA	Medical Dictionary for Regulatory Activities
MHIS	Modified Hachinski Ischemic Scale
MMRM	mixed-model repeated-measures
MMSE	Mini-Mental State Examination
MOA	mechanism of action
MRI	magnetic resonance imaging
NIA-AA	National Institute on Aging (NIA) and the Alzheimer's Association (AA)
No	number

PCR	polymerase chain reaction
PET	positron emission tomography
PHF	paired helical filament deposits
PK/PD	pharmacokinetics/pharmacodynamics
PPS	per-protocol set: The set of data generated by the subset of patients who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
Q2WK	once every 2 weeks
Q4WK	once every 4 weeks
QD	once a day
QW	once a week
QT	QT interval on the ECG
QTc	corrected QT interval
QTcF	Fridericia's corrected QT interval
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SHSF	Self-Harm Supplement form
SPF	skin protection factor
SUSARs	suspected unexpected serious adverse reactions
TE	treatment-emergent
TEADA	treatment-emergent anti-drug antibody
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
V	visit

WBC	white blood cell
Wk	week
WOCBP	women of child-bearing potential

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a,b]	**Clinical Chemistry**[a,b,c]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Total bilirubin
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase (ALP)
Neutrophils, segmented	Alanine aminotransferase (ALT)
Lymphocytes	Aspartate aminotransferase (AST)
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Creatinine
Basophils	Uric acid
Platelets	Calcium
	Glucose, nonfasting
Urinalysis[a,b]	Albumin
Specific gravity	Cholesterol
pH	Creatine kinase (CK)
Protein	**Other Tests**
Glucose	Human chorionic gonadotropin (HCG) (females)[d,e,f]
Ketones	APOE genotyping[a,c,g]
Blood	High sensitivity C-reactive protein[c]
Urine leukocyte esterase	Calculated creatinine clearance (Cockcroft and Gault 1976)
	HBsAg[h]
	HCV RNA PCR[i]
	Immune Safety Labs[i]
	B tryptase
	Total Immunoglobulin E
	Immune complex testing

Abbreviations: RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated (central) laboratory.

[b] Results will be confirmed by the Lilly-designated (central) laboratory at the time of initial testing.

[c] Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

[d] Females of childbearing potential are to have a central lab serum pregnancy test (HCG) at V1. The serum pregnancy test will need to be repeated if the screening period lasts more than 63 days.

[e] Females of childbearing potential are to have a local urine pregnancy test (HCG) on the day of flortaucipir F18 PET imaging before the scan is done to confirm they are not pregnant.

[f] Females of childbearing potential are to have a local urine pregnancy test (HCG) on the day of florbetapir F18 PET imaging before the scan is done to confirm they are not pregnant.

g Neither patients nor investigators will receive the genotype results unless there is a country-specific law or regulation that requires notification of the results. Failure to collect samples for APOE genotyping will not be considered a protocol deviation if country-specific regulations prohibit the testing of genetic material or transportation of such material outside of the country.

h laboratory test to be performed only for patients with a past history of Hepatitis B

i laboratory test to be performed only for patients with a past history of Hepatitis C

j laboratory tests to be performed only for patients with moderate to severe infusion reaction (see Section 9.4.7.1.2 for timing of sample collection).

Appendix 3. Study Governance Considerations

Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. Informed Consent

The investigator is responsible for:

- ensuring that the subject/subject's legal representative understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each subject or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the subject/ subject's legal representative may have throughout the study and sharing in a timely manner any new information that may be relevant to the subjects/ subject's legal representative's willingness to continue his or her participation in the study.
- ensuring that a copy of the ICF is provided to the subject or the subject's legal representative and is kept on file.
- ensuring that the medical record includes a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Study partners will also sign the informed consent. If it is not known that the study partner will change, the new study partner would need to sign the ICF when he/she takes over the care for the subject and study participation. The change in study partner would also need to be documented on the eCRF.

As used in this protocol, the term "informed consent" includes all consent and assent given by subject or their legal representatives and by study partners.

Appendix 3.1.2. Recruitment

Lilly or its designee is responsible for the central recruitment strategy for subjects. Individual investigators may have additional local requirements or processes.

Appendix 3.1.3. Ethical Review

The investigator or an appropriate local representative must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on Good Clinical Practice (GCP).

The study site's ERB(s) should be provided with the following:

- the protocol and related amendments and addenda, current Investigator Brochure (IB) and updates during the course of the study
- informed consent form
- other relevant documents (e.g., curricula vitae, advertisements)

Appendix 3.1.4. Regulatory Considerations

This study will be conducted in accordance with the protocol and with the:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third-party.

Appendix 3.1.5. Investigator Information

Physicians with expertise in neurology, geriatrics, or psychiatry who have clearly documented extensive experience in AD trials will participate as investigators in this clinical study. In addition, licensed clinicians who have clearly documented extensive experience in AD trials may participate as investigators in this clinical study upon approval by the Sponsor. Contact information for investigators, clinical laboratories, and other medical and/or technical department(s) and/or institutions involved in the clinical study is maintained in the study records.

Cognitive assessments must be administered by an individual trained in the use of these instruments. Investigators and site personnel who will perform ratings will be trained and approved by Lilly or its designee prior to participating in the study. In most cases, evaluation and notification will occur at the investigator meeting. Individuals who do not attend the rater evaluation and training portion of the investigator meeting and who wish to perform the ratings in this study must be evaluated and approved by Lilly or its designee prior to performing any ratings. Note that the ADAS-Cog and MMSE must be administered by different rater than the ADCS-ADL and CDR. These 2 raters should continue doing the same scale with the same patient throughout the study. These 2 or 3 raters should continue doing the same scale with the same patient throughout the study. If possible, the measurements should be performed on a given patient by the same rater at each visit. The PI has the responsibility of selecting who will administer the instruments at the site, as long as all training requirements have been met by those raters.

Appendix 3.1.6. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Appendix 3.1.7. Final Report Signature

The CSR coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The investigator with the most qualified subjects will serve as the CSR coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Appendix 3.2. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor investigator study site trainings to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate eCRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the subject data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Appendix 3.2.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Electronic Clinical Outcome Assessment (eCOA) measures (e.g., a rating scale, including audio voice recordings of the rater's questions and the patient's and study partner's responses) are entered into an eCOA instrument (at the time that the information is obtained). The eCOA tablet has both keyboard entry and audio voice recording capabilities. In these instances where there is no prior written or electronic source data at the site, the eCOA instrument record will serve as the source.

If eCOA records are stored at a third party site, investigator sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention.

Any data for which the eCOA instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as audio voice recordings, laboratory test data, or ECG data, will be stored electronically in the central vendor's database system. With the exception of the audio voice recordings, which are only used for central monitoring purposes, data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Any data for which paper documentation provided by the subject will serve as the source document will be identified and documented by each site in that site's study file.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.3.2. Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.4. Publication Policy

The publication policy for Study AACG is described in the Clinical Trial Agreement.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly, or its designee, clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Alkaline Phosphatase Isoenzymes[a]**
CPK	
	Anti-smooth muscle antibody (or anti-actin antibody)[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspirate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

a Assayed by Lilly-designated or local laboratory.

b Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Appendix 5. Flortaucipir F18 Tau PET Imaging

A screening flortaucipir F18 PET scan will be performed as part of the study eligibility criteria. An additional flortaucipir F18 PET scan will be performed at Visit 21 or at early discontinuation (if ED occurs more than 36 weeks after randomization Visit 2).

"Specific instructions for the flortaucipir F18 PET scan itself will be provided in the PET Imaging Manual.

Inclusion Criteria for Flortaucipir F18 PET Scans

With the exception of the MRI and florbetapir F18 PET scan, a patient should meet all other Visit 1 eligibility criteria before having a flortaucipir F18 PET scan.

[1] For female patients of childbearing potential, a negative urine pregnancy (HCG) test must be observed on the day of flortaucipir F18 imaging before beginning imaging procedures.

Exclusion Criteria for Flortaucipir F18 PET Scans

A patient will be excluded from participation in flortaucipir F18 imaging if he or she meets any of the criteria below:

[2] Has any condition that, in the investigator's opinion, could increase risk to the patient, limit the patient's ability to tolerate the experimental procedures, or interfere with analysis of the data. (For example, patients with chronic back pain might not be able to lie still during the scanning procedures.)

[3] Has abnormal findings on physical examination, laboratory screening tests, or screening ECGs that suggest the patient might have a condition that could, in the opinion of the investigator, affect his or her response to the radiopharmaceutical and related testing procedures.

[4] Is deemed likely to be unable to complete the imaging procedure for any reason.

[5] Is receiving other radiation exposure that, when added to the flortaucipir F18 PET scan, would exceed local or national regulatory limits for a patient.

Site investigators, patients, and study partners will not be informed of the results of PET scans obtained following randomization, as they relate to the study. Any findings that may be of potential medical concern will be provided for appropriate follow-up.

PET Scan-Specific Information

PET Scan Procedures

Specific imaging acquisition protocols designed to ensure consistency across sites will be provided in an PET Imaging Manual. The scanning technologists will be blinded to patients' treatment assignments.

Scan Safety

The primary risk related to flortaucipir F18 PET is radiation exposure. Details on the amount of exposure estimated to occur on each imaging occasion and cumulatively are shown in Table APP.5.1 and will be provided in the ICF. In addition, the tau ligand flortaucipir F18 continues to be in clinical evaluation, and risks from the agent are not fully known. Details on the clinical information to date regarding flortaucipir F18 exposure will be provided in the ICF. More detailed information about the known and expected benefits and risks of flortaucipir F18 may be found in the Investigator's Brochure.

Patients must minimize movement during each PET procedure, which can last 10 to 30 minutes for each scan. Most state-of-the-art imaging systems are designed to reduce head motion and patient discomfort.

Table APP.5.1. Effective Radiation Dose (mSv)

	Effective Dose (mSv) per Scan*	Number of Scans in First Year**	Effective Dose (mSv) for Scans in First Year	Number of Scans in Second Year**	Effective Dose (mSv) for Scans in Second Year	Effective Dose (mSv) for – Years 1 and 2
Flortaucipir F 18 Scan (10 mCi iv)	9.10	1	9.10	1	9.10	18.20
Florbetapir F 18 Scan (10 mCi iv)	7.43	2	14.86	2	14.86	29.72
Totals		3	23.96	3	23.96	47.92

Abbreviations: CT = computerized tomography; IV = intravenous infusion; PET = positron emission tomography.

*Dose shown includes radiation exposure from the radiotracer and also assumes a non-clinical CT scan is obtained (estimated at 0.4 mSv) as part of the PET scan attenuation correction process when the scan is done on a PET/CT scanner. A clinical CT scan is not needed during the PET scan session and because it will add additional radiation exposure is not recommended.

** In the event that the patient is discontinued from the Study AACG, the subject will be asked to participate in a discontinuation visit. A flortaucipir F18 scan will not be done at the ET visit if it has been ≤12 weeks since the previous scan.

In the case of early discontinuation from Study AACG, the final flortaucipir F18 PET scan will be obtained at the time of the early discontinuation visit (ED) if at least 36 weeks have passed since the most recent flortaucipir F18 PET scan.

Visits that include imaging should be completed over adjacent days. Note that florbetapir F18 PET amyloid imaging and flortaucipir F18 PET tau imaging can be performed 1 or 2 days after cognitive and functional testing and additional timing considerations apply:

- flortaucipir F18 PET scans should be performed at least 16 hours apart from the florbetapir F18 PET scans due to the half-life of fluorine 18.

With respect to other compound-related risks, flortaucipir was positive in the in vitro hERG assay. Although the margin of safety appears high, and in vivo cardiovascular assessments in dogs showed no evidence of QT prolongation, subjects with a history of risk factors for torsades de pointes and patients taking drugs known to prolong the QT interval will be excluded from this study.

If it becomes necessary for a patient to start taking a medication known to prolong QT interval prior to performance of any postbaseline flortaucipir F18 scan, do not perform the scan. The patient may, however remain in the study. Nonperformance of postbaseline flortaucipir F18 PET scans in patients taking a medication known to prolong QT interval will not be considered a protocol deviation.

Appendix 6. Florbetapir F18 Amyloid PET Imaging

Screening florbetapir F18 PET scans will be performed as part of the study eligibility criteria to determine patient eligibility for participation in Study AACG. Additional florbetapir F18 PET scans will be performed at Visit 8 (Week 24), Visit 15 (Week 52), and Visit 21 (Week 76) or at early discontinuation (if ED occurs more than 8 weeks after the previous visit at which a florbetapir F18 PET scan was done). Specific instructions for the florbetapir F18 PET scan itself will be provided in the PET Imaging Manual.

Inclusion Criteria for Florbetapir F18 PET Scans

With the exception of the MRI, a patient should meet all other Visit 1 eligibility criteria before having a florbetapir F18 PET scan.

[1] For female patients of childbearing potential, a negative urine pregnancy (HCG) test must be observed on the day of florbetapir F18 PET imaging before beginning imaging procedures.

Exclusion Criteria for Florbetapir F18 PET Scans

A patient will be excluded from participation in florbetapir F18 PET amyloid imaging if he or she meets any of the criteria below:

[2] Has any condition that, in the investigator's opinion, could increase risk to the patient, limit the patient's ability to tolerate the experimental procedures, or interfere with analysis of the data. (For example, patients with chronic back pain might not be able to lie still during the scanning procedures.)

[3] Has abnormal findings on physical examination, laboratory screening tests, or screening MRI or ECGs that suggest the patient might have a condition that could, in the opinion of the investigator, affect his or her response to the radiopharmaceutical and related testing procedures.

[4] Is deemed likely to be unable to complete the imaging procedure for any reason.

[5] Is receiving other radiation exposure that, when added to the florbetapir F18 PET scan, would exceed local or national regulatory limits for a patient.

Site investigators, patients, and study partners will not be informed of the results of PET scans obtained following randomization, as they relate to the study. Any findings that may be of potential medical concern will be provided for appropriate follow-up.

PET Scan-Specific Information

PET Scan Procedures

Specific imaging acquisition protocols designed to ensure consistency across sites will be provided in a PET Imaging Manual. The scanning technologists will be blinded to patients' treatment assignments.

PET Scan Safety

The primary risk related to florbetapir F18 PET is radiation exposure. Details on the amount of exposure estimated to occur on each imaging occasion and cumulatively are presented in Table APP.5.1 above and will be provided in the ICF. Details on the clinical information to date regarding florbetapir F18 exposure will be provided in the ICF. More detailed information about the known and expected benefits and risks of florbetapir F18 may be found in the United States Package Insert for florbetapir F18 Injection (Amyvid™).

Patients must minimize movement during each PET procedure, which can last 10 to 30 minutes for each scan. Most state-of-the-art imaging systems are designed to reduce head motion and patient discomfort.

In the case of early discontinuation from Study AACG, the final florbetapir F18 PET scan will be obtained at the time of the early discontinuation visit (ED) if at least 8 weeks have passed since the most recent florbetapir F18 PET scan.

Visits that include imaging should be completed over adjacent days. Note that florbetapir F18 PET amyloid imaging and flortaucipir F18 PET tau imaging can be performed 1 or 2 days after cognitive and functional testing and additional timing considerations apply:

- florbetapir F18 PET scans should be performed at least 16 hours apart from the flortaucipir F18 PET scan due to the half-life of fluorine 18.

Appendix 7. Protocol Amendment [I5T-MC-AACG(c)] Summary [Assessment of Safety, Tolerability, and Efficacy of LY3002813 in Early Symptomatic Alzheimer's Disease]

Overview

Protocol I5T-MC-AACG Assessment of Safety, Tolerability, and Efficacy of LY3002813 in Early Symptomatic Alzheimer's Disease has been amended. The new protocol is indicated by amendment (d) and will be used to conduct the study in place of any preceding version of the protocol.

The main changes to this protocol include removing LY3202626 as a combination therapy.

The overall changes and rationale for the changes made to this protocol are described in the following table. Note that minor edits have been made throughout the protocol, which are not captured in the amendment summary table.

Amendment Summary for Protocol I5T-MC-AACG Amendment (d)

Section # and Name	Description of Change	Brief Rationale
Title page	Removed mention of LY3202626 and combination therapy. Added amendment (d) to the list of amendments. Changed date of current protocol.	To reflect the content of the current amendment.
Section 1. Synopsis	Changed study title and removed mention of LY3202626 and combination therapy from the study description and the study objectives. Changed numbers of patients to reflect the elimination of the LY3202626 treatment arm. Deleted the row for "Evaluable" under "Approximate Number of Patients."	To reflect the elimination of the LY3202626 treatment arm. Deleted to prevent confusion. Details are provided in Section 10.
Section 2. Schedule of Activities	Removed ophthalmological and dermatological exams from screening assessments and changed timing of these assessments during the treatment period to reflect the elimination of the LY3202626 treatment arm. Removed mention of LY3202626 administration, compliance checks, and plasma PK sampling. Deleted the column for Visit 22, as this visit is no longer needed.	To reflect the elimination of the LY3202626 treatment arm.
Section 3. Introduction	Removed mention of LY3202626 as part of the combination. Removed background specific to LY3202626 and its mechanism of action.	To reflect the elimination of the LY3202626 treatment arm.
Section 3.2.2. LYL3002813 Phase 1 Studies	Updated information about ongoing Phase 1b single- and multiple-dose study I5T-MC-AACD (Study AACD).	To provide updated information about this ongoing study.
Section 4. Objectives and Endpoints	Removed mention of LY3202626 and combination therapy from the study objectives. Removed ophthalmological and dermatological examinations from safety endpoints.	To reflect the elimination of the LY3202626 treatment arm.
Section 5. Study Design	Removed mention of LY3202626 and combination therapy from the study design. Added description of screening policy for patients in active screening	To reflect the elimination of the LY3202626 treatment arm.

Section # and Name	Description of Change	Brief Rationale
	prior to implementation of amendment (d). Changed duration of double-blind period to 76 weeks, with up to 72 weeks of treatment. Modified study design illustration and visits throughout. Changed number of study participants. Removed ophthalmological and dermatological evaluation from Screening.	 To delete examinations and visit no longer needed after elimination of the LY3202626 treatment arm.
Section 5.1. Overall Design	Changed "124-week study" to "133-week study."	Correction
Section 5.1.3. Immunogenicity and Safety Follow-up Visits (Visit 801)	Changed heading to "Immunogenicity and Safety Follow-up Visits (Visits 801 through 804)"	Clarification (made consistent with text)
Section 6.1. Inclusion Criteria	From Inclusion Criterion #4, deleted the bullet regarding study partners being available by telephone for CDR and ADCS-ADL.	Correction; this scale is not administered over the phone.
Section 6.2. Exclusion Criteria	From Exclusion Criterion #11, deleted "retinal" from the list of exclusionary conditions. Deleted Exclusion Criterion #18, #32, #37, #56, and #57.	To remove criteria specific to LY3202626.
Section 6.3. Lifestyle Restrictions	Restrictions #2 and #3 were removed.	To remove restrictions specific to LY3202626.
Section 7. Treatments	Deleted mention of LY3202626 dosage, administration, and packaging.	To reflect the elimination of the LY3202626 treatment arm.
Section 8. Discontinuation Criteria	Deleted ophthalmological and dermatological examinations as a factor in permanent treatment discontinuation. Rephrased discontinuation to remove mention of discontinuing one treatment but continuing the other. Deleted criteria specific to discontinuing treatment with LY3202626. Changed timing of follow-up after early discontinuation visit.	To reflect the elimination of the LY3202626 treatment arm.
Section 9. Study Assessments and Procedures	Deleted administration of LY3202626. Removed AESIs specific to LY3202626. Deleted information	To reflect the elimination of the LY3202626 treatment arm.

Section # and Name	Description of Change	Brief Rationale
	about treatment of LY3202626 overdose. Edited text about ophthalmological and dermatological examinations to clarify that these will be done only in patients who received LY3202626 or oral placebo and only at 1 visit (scheduled or unscheduled) after the final dose of LY3202626/oral placebo. Deleted information about PK sampling for LY3202626. Added statements about completing CRFs for hypersensitivity and ARIA-E. In Section 9.1 (and Appendix 3.1.5), changed the statement that ADAS-Cog and MMSE "should" be administered by a different rater than ADCS-ADL and CDR to "must" be administered by a different rater.	 Clarification Clarification
Section 10. Statistical Considerations	Changed numbers of patients and power calculations to reflect the elimination of the LY3202626 treatment arm. Deleted mentions of combination therapy. Provided information about how data from patients previously randomized to LY3202626 treatment will be handled.	To reflect the elimination of the LY3202626 treatment arm.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

The numbering system used for inclusion and exclusion criteria provides a unique number for each criterion and allows for efficiency in data collection.

In case an amendment to the protocol adds a criterion, that criterion will receive the next available number, regardless of whether it is an inclusion or exclusion criterion.

Title Page

Protocol I5T-MC-AACG(d~~c~~) Assessment of Safety, Tolerability, and Efficacy of LY3002813 ~~Alone and in Combination with LY3202626~~ in Early Symptomatic Alzheimer's Disease

Confidential Information

The information contained in this document is confidential and is intended for the use of clinical investigators. It is the property of Eli Lilly and Company or its subsidiaries and should not be copied by or distributed to persons not involved in the clinical investigation of LY3002813 ~~and LY3002813/LY3202626 combination~~, unless such persons are bound by a confidentiality agreement with Eli Lilly and Company or its subsidiaries.

LY3002813

~~&~~

~~LY3202626~~

Multicenter, randomized, double-blind, placebo-controlled, Phase 2 study comparing up to 1400 mg of LY3002813 ~~alone and in combination with 12 mg of LY3202626~~ with placebo over 76~~80~~ weeks in approximately 250~~300~~ patients with early symptomatic AD.

Section 1. Synopsis

Title of Study:

Protocol I5T-MC-AACG(c). Assessment of Safety, Tolerability and Efficacy of LY3002813 ~~Alone and in Combination with LY3202626~~ in Early Symptomatic Alzheimer's Disease.

Rationale:

~~This study evaluates use of two anti-amyloid therapies with different mechanisms of action targeting the amyloid cascade.~~ LY3002813 is an antibody directed at the pyroglutamate modification of the third amino acid of amyloid beta (N3pG Aβ) epitope that is present only in brain amyloid plaques. It is being studied for the treatment of Alzheimer's disease (AD). The mechanism of action of LY3002813 is considered to be the targeting and removal of existing amyloid plaque, which is a key pathological hallmark of AD. The clinical strategy for LY3002813 targets the N3pG Aβ specific to amyloid plaque in the population of early symptomatic AD patients with existing brain amyloid load, as measured using the amyloid plaque biomarker, florbetapir F18 positron emission tomography (PET) imaging. This~~LY3202626 is a synthetic small molecule, an inhibitor of β-site amyloid precursor protein (APP)-cleaving enzyme [BACE]1, being assessed for the treatment of AD in an ongoing phase 2 study. The mechanism of action of LY3202626 is considered to be the reduction of Aβ monomer production through BACE 1 inhibition. Combination therapy~~ rationale is based on the amyloid hypothesis of AD, which states that the production and deposition of Aβ is an early and necessary event in the pathogenesis of AD (Selkoe 2000). Clinical support for this hypothesis comes from the demonstration that parenchymal Aβ levels are elevated before the appearance of symptoms of AD, and supported by genetic variants of AD that overproduce brain Aβ and genetic variants that protect against Aβ production (Jonsson et al. 2012; Fleisher et al. 2015). Furthermore, early in the disease, the presence of brain amyloid appears to increase the risk of conversion from mild cognitive impairment (MCI) to AD dementia (Doraiswamy et al. 2012). This suggests that enhanced clearance of Aβ will lead to slowing of AD progression.

~~This study, I5T-MC-AACG (AACG), is evaluating LY3002813 alone or in combination with LY3202626 compared with placebo. There is evidence suggesting that different forms of amyloid (monomeric, oligomeric and insoluble plaques) may all contribute neurotoxicity independently (Selkoe 2008). Animal models suggest that treatment with a combination of a BACE inhibitor and an anti-plaque antibody will reduce soluble forms of amyloid and contribute to a greater reduction of deposited plaques compared with a plaque-specific antibody alone (Jacobsen et al. 2014). This may also provide synergistic effects on plaque removal compared to either drug given independently with more rapid and quantitatively greater amyloid removal (DeMattos 2016). Increased and more rapid removal of amyloid plaque plus removal of soluble forms of amyloid by parallel administration of both LY3002813 and LY3202626 over time is therefore hypothesized to have the potential for greater clinical efficacy than either drug given alone, with broader target engagement. Combination of therapeutics has been standard of care in most disease clinical practices, such as oncology, cardiology, and endocrinology. Of late, there has been much discussion of the need for combination therapies in AD, as an ultimate path toward finding beneficial treatments for patients (Hendrix 2016).~~

Study I5T-MC-AACG (AACG) is a Phase 2, double-blind, placebo-controlled, study to evaluate the safety and efficacy of N3pG antibody (LY3002813) ~~alone or in combination with BACE inhibitor (LY3202626)~~ in patients with early symptomatic AD (prodromal AD and mild dementia due to AD). Study AACG will assess whether removal of existing amyloid plaque

~~alone or in combination with lowering of Aβ production via BACE inhibition~~ can slow the progression of disease as assessed by clinical measures and biomarkers of disease pathology and neurodegeneration over up to 72~~76~~ weeks of treatment.

Multiple biomarkers of disease progress will also be evaluated. The biomarker florbetapir F18 is a PET ligand that binds to fibrillar amyloid plaque. This biomarker can provide a qualitative and quantitative measurement of brain plaque load in patients with prodromal AD or mild AD dementia. The absence of significant florbetapir F18 signal on a visual read indicates that those patients clinically manifesting cognitive impairment have sparse to no amyloid plaques. As such, implementation of florbetapir F18 will provide a screening tool for entry into the clinical trial~~trials~~ and provide a confirmation of amyloid pathology. Florbetapir F18 PET also provides quantitative assessment of fibrillar amyloid plaque in the brain and can assess amyloid plaque reductions from the brain by LY3002813 ~~and in combination with BACE inhibition with LY3202626~~.

Objective(s)/Endpoints:

Primary Objective	**Primary Endpoint**
To test the hypothesis that LY3002813 ~~alone and/or in combination with LY3202626~~ administered for up to 72~~76~~ weeks will decrease the cognitive and/or functional decline in patients with early symptomatic AD	Change in cognition and function as measured by the change in integrated Alzheimer's Disease Rating Scale (iADRS) score from baseline to 18 months
Secondary Objectives To assess the effect of LY3002813 ~~alone and in combination with LY3202626~~ vs. placebo~~s~~ on clinical progression in patients with early symptomatic AD	**Secondary Endpoints** Change in cognition from baseline to 18 months as measured by: • the change in Alzheimer's Disease Assessment Scale—Cognitive subscale (ADAS-Cog_{13}) score • the change in Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) score • the change in Mini-Mental State Examination (MMSE) score • the change in Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living scale (ADCS-iADL) score
To assess the effect of LY3002813 ~~alone and in combination with LY3202626~~ vs. placebo on brain amyloid deposition	Change in brain amyloid plaque deposition from baseline through 18 months as measured by florbetapir F18 PET scan
To assess the effect of LY3002813 ~~alone and in combination with LY3202626~~ vs. placebo on brain tau deposition	Change in brain tau deposition from baseline to 18 months as measured by flortaucipir F18 PET scan
To assess the effect of LY3002813 ~~alone and in combination with LY3202626~~ vs. placebo on brain volume measures	Change in volumetric MRI measures from baseline to 18 months.

~~To assess the effect of combination therapy with LY3002813 and LY3202626 vs LY3002813 alone on clinical progression in patients with early symptomatic AD~~	~~Change from baseline to 18 months in iADRS score, ADAS-Cog$_{13}$ score, CDR-SB score, MMSE score, ADCS-iADL score~~
Safety Objective	**Safety Endpoints**

To evaluate safety and tolerability of LY3002813 ~~alone and in combination with LY3202626~~	• Standard safety assessments:
	  ○ spontaneously reported adverse events (AEs)
	  ○ clinical laboratory tests
	  ○ vital sign and body weight measurements
	  ○ 12-lead ECGs
	  ○ physical and neurological examinations
	• MRI (amyloid-related imaging abnormalities [ARIAs] and emergent radiological findings)
	• ~~Skin examination~~
	• ~~Eye examination~~
	• Columbia Suicide Severity Rating Scale (C-SSRS)

Summary of Study Design:

Study AACG is a multicenter, randomized, double-blind, placebo-controlled, Phase 2 study of LY3002813 ~~alone and in combination with LY3202626~~ in subjects with early symptomatic AD. The 133~~124~~-week study includes a screening period of up to 9 weeks, a treatment period of up to 72~~76~~ weeks with final evaluations occurring 4 weeks later at Week 76, and ~~,~~ a 48~~4-week posttreatment follow-up, and a 44~~-week immunogenicity and safety follow-up period.

Treatment Arms and Duration:

Patients will receive the following treatments for up to 72~~76~~ weeks:

- LY3002813 ~~monotherapy (**LY3002813-M**)~~: intravenous LY3002813 (700 mg Q4WK for the first 3 doses, then 1400 mg Q4WK) for up to 72 weeks~~,in combination with daily oral placebo,~~
- ~~LY3002813 in combination with LY3202626 (**LY3002813-C**): intravenous LY3002813 (700 mg Q4WK for the first 3 doses, then 1400 mg Q4WK) in combination with daily oral LY3202626 (12 mg),~~ or
- **Placebo**: intravenous placebo Q4WK for up to 72 weeks~~in combination with daily oral placebo~~.

~~Abbreviations: C = combination therapy; M = monotherapy~~

Approximate Number of Patients:

Screened – 1497

Randomized – 266~~375~~

~~Evaluable – 300 (approximately 100 per treatment group)~~

Statistical Analysis:

Efficacy:

The primary objective of this study is to test the hypothesis that intravenous infusion of LY3002813 ~~alone or in combination with LY3202626~~ will slow the cognitive and/or functional decline of AD as measured by the composite measure iADRS compared with placebo in patients with early symptomatic AD. The change from baseline score on the iADRS at each scheduled postbaseline visit during the treatment period will be analyzed using an MMRM model, which includes the following terms: baseline score, pooled investigator, treatment, visit, treatment-by-visit interaction, baseline-by-visit interaction, concomitant AChEI and/or memantine use at baseline (yes/no), and age at baseline. The primary time point for treatment comparison will be at the end of the double blind treatment period (Week 76). The treatment group contrast in least-squares mean progression and its associated p-value and 95% CI will be calculated for the treatment comparison of LY3002813 ~~-C~~ vs. placebo ~~and LY3002813-M vs. placebo~~. In addition, Bayesian posterior probability of the active treatment arm being superior to placebo by at least a margin of interest (25% slowing of placebo progression) will also be calculated.

Pharmacokinetics/Pharmacodynamics:

Compartmental modeling of LY3002813 ~~and LY3202626~~ PK data using nonlinear mixed effects modeling or other appropriate software may be explored, and population estimates for clearance and central volume of distribution may be reported. Depending on the model selected, other PK parameters may also be reported. Exploratory graphical analyses of the effect of dose level or demographic factors on PK parameters may be conducted. If appropriate, data from other studies of LY3002813 ~~or LY3202626~~ may be used in this analysis.

Pharmacokinetic/pharmacodynamic (PK/PD) relationships between plasma LY3002813 concentration and SUVr, cognitive endpoints, ARIA incidence rate or other markers of PD activity may be explored graphically. The relationship between the presence of antibodies to LY3002813 and PK, PD, safety and/or efficacy may be assessed graphically. ~~The effect of LY3202626 exposure on SUVr, cognitive endpoints, or other markers of PD activity may also be explored graphically. Graphical and/or descriptive analyses may be explored to evaluate potential interactions between LY3002813 and LY3202626 for PK.~~ If warranted, additional analysis may be explored to evaluate potential interactions for ADA, PD and other endpoints (PET scan, ARIA-E, etc.). Additional modeling may be performed based on the results of the graphical analyses.

Section 2. Schedule of Activities

Schedule of Activities Protocol - I5T-MC-AACG Visit 1 (Screening Period)

Period: Procedure	
Visit No.:	**V1**
End of Week Relative to Study Medication Start[a]	**Wk -9 through Wk -1**
Tolerance Interval for Visit (days)[a,b]	**63**
PRELIMINARY SCREENING	
Entry Diagnostics	
MMSE[c,d,su]	X
SCREENING	
~~Ophthalmological examination~~[f]	~~X~~
~~Dermatological examination~~[g]	~~X~~
Safety Assessments	
Vital signs[fh]	X
Height and ~~W~~weight[gi]	X
ECG in triplicate[hj]	X
C-SSRS/SHSF/SHFU[i,ik,l]	X
Laboratory Specimens	
Human chorionic gonadotropin (HCG) (if applicable)[k,l,m,n,o]	X[b]
HBsAg[np]	X
HCV RNA PCR[oq]	X
Screening PET Scans and MRI	
Flortaucipir F18 PET ~~S~~scan[l,pn,r]	X
MRI[qs]	X
Florbetapir F18 PET scan[b,m,ro,t]	X

Abbreviations: HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; MRI = ~~M~~magnetic ~~R~~resonance ~~I~~imaging; PCR = polymerase chain reaction; SHFU = Self-Harm Follow-Up.

[a] The interval between V1 and V2 may be up to 63 days to allow for completion of V1 screening procedures, assessments, and evaluation of results from laboratory tests and ECGs. V1 is not considered complete until all screening procedures have been completed and results reviewed by the investigator to determine patient eligibility. V1 may be conducted over more than 1 day. Subjects in screening at the time screening was paused are allowed to continue screening beyond the 63 days to allow for completion of V1 screening procedures; this will not be a protocol deviation. Additional details are provided in Section 5.1.1. Subjects who had completed screening but were not yet randomized at the time randomization was paused are allowed to be randomized beyond 63 days; this will not be a protocol deviation. Additional details are provided in Section 5.1.1.

[b] A florbetapir F18 PET scan is the final screening criterion for establishing patient eligibility, although the MRI~~, ophthalmological and dermatological exams~~ may be performed after the florbetapir F18 PET scan. Patients whose screening florbetapir F18 PET scan results are not available within the 63 day screening window will remain eligible within V1 until these results become available if all other eligibility criteria have been met. Note: If a patient's screening florbetapir F18 PET scan result confirming eligibility for the study has not been received by the site by Day 63 of the screening period, then repeat the following laboratory tests: blood hematology, chemistry, and serum pregnancy test (HCG) for women of childbearing potential (WOCBP). Results of the repeated labs are to be reviewed by the investigator or qualified designee for assessment of the patient's continued eligibility. Repeat screening for MMSE, CBB, C-SSRS, ECG~~, dermatological and ophthalmological examinations~~, flortaucipir F18 PET, MRI, and laboratory testing for HBsAg, and HCV RNA PCR is not required. V1 is not considered complete until all screening procedures have been completed and results reviewed by the investigator or qualified designee to determine patient eligibility.

[c] A preliminary screening informed consent may be obtained to conduct initial screening to collect demographics data and administer the MMSE and CBB. Patients who do not meet the MMSE screening criteria are not to have any other screening procedures performed with the exception of the CBB. The CBB should be administered to all patients at the screening visit, regardless of the MMSE score. They may be rescreened for the MMSE 8 weeks after the first screen. Study partners are not required to complete the preliminary screening informed consent.

[d] Patients who meet the MMSE screening criteria may proceed to the remaining screening procedures once they have given signed/dated informed consent for the full study and their study partner has given signed/dated informed consented to participate as a study partner.

[e] A complete physical and neurological exam is to be performed at this visit. Additional details are provided in Section 9.4.1.

~~[f] Eye examinations must be conducted by an ophthalmologist or optometrist (where permitted by law). Additional details are provided in Section 9.4.6.3.~~

~~[g] Skin examinations must be conducted by a dermatologist. Additional details are provided in Section 9.4.6.4~~

[~~f~~h] Sitting ~~B~~blood pressure and pulse will be measured after 5 minutes in the sitting position only. Temperature will be collected with sitting vital signs.

[~~g~~i] Height and weight will be measured with shoes removed.

[~~h~~j] ECGs should be taken in triplicate at approximately 1-minute intervals. ECGs should be collected at approximately the same time of day, as much as possible, to minimize diurnal variation.

[~~i~~k] The baseline version of the C-SSRS is to be administered at V1. Patients at imminent risk of suicide (positive response to question 4 or 5 on the C-SSRS) will be excluded from participating in the study.

~~j~~i The ~~Self-Harm Supplement form~~SHSF is completed after each C-SSRS administration to enter the number of discrete events of suicidal behavior identified. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, then the ~~Self Harm Follow-Up (~~SHFU~~)~~ form will be used to collect additional information to allow for a more complete assessment of these behaviors.

~~k~~m Females of childbearing potential are to have a serum pregnancy test (HCG) at V1 (if applicable).

~~l~~n Females of childbearing potential are to have a urine pregnancy test (HCG) on the day of flortaucipir F18 PET imaging before the flortaucipir F18 dose is administered.

~~m~~o Females of childbearing potential are to have a urine pregnancy test (HCG) on the day of florbetapir F18 PET imaging before the florbetapir F18 dose is administered.

~~n~~p Patients with a past history of Hepatitis B are to have a serum HBsAg test at screening V1 and are excluded if the HBsAg test is positive.

~~o~~q Patients with a past history of Hepatitis C are to have a HCV RNA PCR test at screening V1 and are excluded if the HCV RNA PCR test is positive.

~~p~~r A screening flortaucipir F18 PET scan will be performed as part of the study eligibility criteria at all sites to determine patient eligibility for participation in Study AACG (see Appendix 5). With the exception of an MRI and a florbetapir F18 PET scan, ~~ophthalmological, and dermatological exams,~~ a patient should meet all other V1 eligibility criteria before having a screening flortaucipir F18 PET scan. The flortaucipir F18 PET scan will be submitted to a centralized PET imaging vendor designated by Lilly for an assessment of patient's eligibility. A historical flortaucipir F18 PET scan may be submitted to be considered for eligibility if performed within 6 months of V1.

~~q~~s A local screening MRI will be performed at V1 as part of the study eligibility criteria. With the exception of the evidence of amyloid pathology by florbetapir F18 PET scan, ~~and ophthalmological and dermatological exams,~~ a patient should meet all other V1 eligibility criteria before having an MRI scan. The MRI scans will be reviewed by the investigator or qualified designee for immediate patient management. After the MRI scan is read locally, the scan is to be submitted to the centralized MRI vendor designated by Lilly for final determination of MRI eligibility. Results of centrally read MRIs will be used for data analysis and report-writing purposes and patient safety and eligibility will be reported back to sites.

~~r~~t A screening florbetapir F18 PET scan will be performed as part of the study eligibility criteria to determine patient eligibility for participation in Study AACG (see Appendix 6). With the exception of an MRI ~~and ophthalmological and dermatological exams~~, a patient should meet all other V1 eligibility criteria before having a screening florbetapir F18 PET scan. The PET scan will be submitted to a centralized PET imaging vendor designated by Lilly for assessment of patient's eligibility. The florbetapir F18 PET screening criteria must be met (scan results consistent with the presence of amyloid pathology) in order for the patient to proceed to V2 and be randomized to treatment assignment.

~~s~~u Assessment is to include the audio voice recording of the rater's questions and the patient and caregiver responses to assessment questions.

Schedule of Activities, Protocol I5T-MC-AACG, Visit 2 through Visit 14 (Double-Blind Period)

Period: / Procedure	Rand												
Visit No.:	**V2[a,b]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**
End of Week Relative to Study Medication Start	0	4	8	12	16	20	24	28	32	36	40	44	48
Tolerance Interval for Visit (days)	0	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Inclusion/exclusion review	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IWRS – dispensation of study medication (LY3002813 ~~and LY3202626~~)	X[e]	X	X	X	X	X	X	X	X	X	X	X	X
Physical/neurological examination[ef]	X[fg]			X[fg]			X[fg]			X[gh]			
Ophthalmological examination[hi]	~~j~~[k]			X[h]				X[h]					~~X~~
Dermatological examination[ij]	~~j~~[k]			X[i]			X[i]						
Previous/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Preexisting conditions/adverse events[ef]	X	X	X	X	X	X	X	X	X	X	X	X	X
LY3002813 study medication administered[k] ~~Assess LY3202626 compliance~~	X	X	X	X	X	X	X	X	X	X	X	X	X
~~LY3202626 study medication administered at site~~ [t]		~~X~~			~~X~~								
~~LY3002813 Study medication administered~~[l]	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~
Efficacy Measures													
ADAS-Cog$_{13}$[l,ff~~m,jj~~]	X			X			X			X			
ADCS-ADL[l,ff~~m,jj~~]	X			X			X			X			
CDR-SB[l,ff~~m,jj~~]	X			X			X			X			
MMSE[l,ff~~m,jj~~]				X			X			X			
Safety Assessment													
C-SSRS/SHSF/SHFU[m,n~~o~~]	[m~~n~~]	X	X	X	X	X	X	X	X	X	X	X	X

Schedule of Activities, Protocol I5T-MC-AACG, Visit 2 through Visit 14 (Double-Blind Period)

Period: / Procedure	Rand												
Visit No.:	**V2[a,b]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**
End of Week Relative to Study Medication Start	0	4	8	12	16	20	24	28	32	36	40	44	48
Tolerance Interval for Visit (days)	0	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Laboratory Specimens[op]													
Clinical chemistry, hematology[pq]	X	X	X	X			X			X			
High sensitivity C-reactive protein[pq]	X	X	X	X			X			X			
Urinalysis[pq]	X												
Serum for anti-LY3002813 antibody[pq]	X	X	X	X	X		X			X			
Serum LY3002813[q,rr,ss]	X[q]	X[rs]	X[rs]	X[qr]	X[rs]		X[qr]			X[rs]			
~~Plasma LY3202626[t,u,v]~~		~~X[t,u]~~	~~X[v]~~	~~X[v]~~	~~X[t,u]~~		~~X[v]~~			~~X[v]~~			
Blood for assessment of APOE genotype[p,sq,w]	X												
Whole blood, plasma and serum for biomarker storage[p,tq,x]	X			X			X			X			
Blood for pharmacogenomics[p,t,uq,x,y]	X												
Other Safety Measures													
Weight	X			X			X			X			
Vital signs and temperature[v,wz,aa]	X[waa]	X	X	X[waa]	X	X	X[waa]	X	X	X[waa]	X	X	X
ECG in triplicate[xbb]	X	X	X	X			X			X			
MRI[yee]	~~zdd~~	X		X[aaee]	X		X			X			
Additional Efficacy Measures													
Flortaucipir F18 PET scan[bb,ccff,gg]	~~zdd~~												
Florbetapir F18 PET scan[bb,ddff,hh]	~~zdd~~						X[bb,ddff,~~hh~~]						

Schedule of Activities, Protocol I5T-MC-AACG, Visit 15 through Visit 21~~22~~ (Double-Blind Period) and Follow-Up

Period: / Procedure										
Visit No.:	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**~~V22~~**	**ED[c]**	**V801-V804[d,ee~~ii~~]**
End of Week Relative to Study Medication Start	52	56	60	64	68	72	76	~~80~~		88-124
Tolerance Interval for Visit (days)	±7	±7	±7	±7	±7	±7	±7	~~±7~~		±14
Inclusion/exclusion review	X	X	X	X	X	X	~~X~~			
Contact IWRS – dispensation of study medications (LY3002813 ~~and LY3202626~~)	X	X	X	X	X	X				
Physical/neurological examination[e~~f~~]	X[f~~g~~]			X[g~~h~~]			X[f~~g~~]	~~X~~[g]	X[f~~g~~]	
Ophthalmological examination[h,~~ii~~]					~~X~~			~~X~~	X[h]	
Dermatological examination[i,~~jj~~]	~~X~~							~~X~~	X[i]	
Previous/concomitant medications	X	X	X	X	X	X	X	~~X~~	X	~~X~~
Preexisting conditions/adverse events[e~~f~~]	X	X	X	X	X	X	X	~~X~~	X	~~X~~
~~Assess LY3202626 compliance~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~		~~X~~	
LY3002813 ~~S~~study medication administered[k~~l~~]	X	X	X	X	X	X				
Efficacy Measures										
ADAS-Cog$_{13}$[l,~~ff~~m,~~jj~~]	X			X			X		X	
ADCS-ADL[l,~~ff~~m,~~jj~~]	X			X			X		X	
CDR-SB[l,~~ff~~m,~~jj~~]	X			X			X		X	
MMSE[l,~~ff~~m,~~jj~~]	X			X			X		X	
Safety Assessment										
C-SSRS/SHSF/SHFU[m,n~~o~~]	X	X	X	X	X	X	X	~~X~~	X	X

Schedule of Activities, Protocol I5T-MC-AACG, Visit 15 through Visit 2122 (Double-Blind Period) and Follow-Up

Period: / Procedure										
Visit No.:	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**~~V22~~**	**ED[c]**	**V801-V804[d,ee~~ii~~]**
End of Week Relative to Study Medication Start	52	56	60	64	68	72	76	~~80~~		88-124
Tolerance Interval for Visit (days)	±7	±7	±7	±7	±7	±7	±7	~~±7~~		±14
Laboratory Specimens[op]										
Clinical chemistry, hematology[pq]	X			X			X	~~X~~	X	
High sensitivity C-reactive protein[pq]	X			X			X	~~X~~	X	
Urinalysis[pq]	X			X			X	~~X~~	X	
Serum for anti-LY3002813 antibody[pq]	X						X		X	X
Serum LY3002813[p,q,rr,s]	X[qr]			X[rs]		X[qr]	X[rs]		X[rs]	X[rs]
~~Plasma LY3202626[t,u,v]~~	~~X[v]~~			~~X[v]~~			~~X[v]~~		~~X[v]~~	
Blood for assessment of APOE genotype[p,sq,w]										
Whole blood, plasma and serum for biomarker storage[p,tq,x]	X			X			X		X	
Blood for pharmacogenomics[p,t,uq,x,y]										
Other Safety Measures										
Weight	X			X			X	~~X~~	X	
Vital signs and temperature[v,wz,aa]	X[waa]	X	X	X[waa]	X	X	X[waa]	~~X[aa]~~	X ~~X[aa]~~	~~X~~
ECG in triplicate[xbb]	X			X			X	~~X~~	X	
MRI[yee]	X						X		X	
Additional Efficacy Measures										
Flortaucipir F18 PET Scan[bb,ccff,gg]							X[bb,ccff,~~gg~~]		X[bb,ccff,~~gg~~]	
Florbetapir F18 PET scan[bb,ddff,hh]	X[bb,ddff,~~h~~]						X[bb,ddff,~~hh~~]		X[bb,ccff,~~gg~~]	

Schedule of Activities, Protocol I5T-MC-AACG, Visit 2 through Visit 21~~22~~ (Double-Blind Period) and Follow-Up Abbreviations and Footnotes

Abbreviations: APOE = a~~A~~polipoprotein subtype E; ARIA-E = amyloid related imaging abnormalities–edema/effusions

[a] Confirm that the patient has met all V1 eligibility criteria before proceeding with V2 procedures.

[b] At V2, appointments should be made for all remaining visits and should be scheduled as close as possible to the target date, relative to V2. Procedures for some visits may take more than 1 day.

[c] If a patient discontinues before the double-blind period endpoint (V21~~V22~~ at Week 76~~80~~), complete the Early Discontinuation CRFs. The patient should be encouraged to return to the site beginning 12 weeks after the ED visit for an immunogenicity follow-up visit (V~~isit~~ 801 through V804).

[d] Patients are to return to the site for collection of blood samples and safety assessments for assessment of immunogenicity status at V~~isit~~ 801 (Week 88). Follow-up for patients experiencing clinically significant events associated with TEADA status is described in Section 9.4.7.2.

~~[e] Patients are to take oral study medication (placebo or LY3202626) once per day in the morning. The first dose should be taken the morning after the first dispensing of oral study medication at Visit 2.~~

[e~~f~~] Any clinically significant changes from baseline on follow-up physical/neurological examinations should be noted on the AE page.

[f~~g~~] A complete physical and neurological exam is to be performed at this visit. Additional details are provided in Section 9.4.1.

[g~~h~~] A brief physical and neurological exam is to be performed at this visit. Additional details are provided in Section 9.4.1.

[h] ~~Eye~~ Ophthalmological examinations will be performed only in patients who previously received LY3202626/oral placebo in this study. The final examination for each patient will be the next scheduled ophthalmological examination after the final administration of LY3202626/oral placebo. It will not be considered a protocol deviation if this examination is scheduled sooner than indicated above in order to accommodate patient and/or site preference. Patients who received LY3202626/oral placebo after their V9 ophthalmological examination are to have an unscheduled ophthalmological examination at the next available opportunity. These ~~Eye~~ examinations must be conducted by an ophthalmologist or optometrist (where permitted by law). Additional details are provided in Section 9.4.6.3.

[i] Dermatological examinations will be performed only in patients who previously received LY3202626/oral placebo in this study. The final examination for each patient will be the next scheduled dermatological evaluation after the final administration of LY3202626/oral placebo. It will not be considered a protocol deviation if this examination is scheduled sooner than indicated above in order to accommodate patient and/or site preference. Patients who received LY3202626/oral placebo after their V8 dermatological examination are to have an unscheduled dermatological examination at the next available opportunity. These examinations must be conducted by a dermatologist. Additional details are provided in Section 9.4.6.4.

[j] For subjects randomized prior to amendment (d), the ~~eye~~ ophthalmological and ~~skin~~ dermatological examination performed at screening will serve as the baseline ~~eye~~ ophthalmological and ~~skin~~ dermatological examination.

[k~~l~~] Study drug will be administered by intravenous administration at investigative study site. Patients should be observed for approximately 2 hours following each infusion of LY3002813 for the first 6 infusions. After the first six doses, a minimal post-infusion observation time of 60 minutes will be required for all subsequent infusions. However, patients who have had dosing restarted after ARIA-E are required to be monitored for 2 hours following infusion for a minimum of 3 subsequent infusions, and a minimum of 60 minutes post-infusion observation thereafter.

[l~~m~~] When administered, cognitive and functional assessments (ADAS-Cog_{13}, ADCS-ADL, CDR, and MMSE) should be performed first, before medical procedures that could be stressful for the patient (e.g., blood draws).

[m~~n~~] The C-SSRS administered at screening will serve as the baseline C-SSRS.

[no] The 'since last visit' version of the C-SSRS will be administered at visits after V2 (Week 0) to the patient with the study partner/study informant present, after the cognitive and functional assessments. The Self-Harm Supplement form (SHSF) is completed after each C-SSRS administration to enter the number of discrete events of suicidal behavior identified. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, then the SHFU form will be used to collect additional information to allow for a more complete assessment of these behaviors

[op] Unscheduled laboratory tests may be performed at the discretion of the investigator.

[pq] Labs are to be collected prior to administration of the intravenous study medication (LY3002813 or IV placebo). Record the date and times of sample collection on the Lab Requisition Form.

[qr] **Pre-dose** (before beginning the infusion) samples for intravenous study medication (LY3002813) may be collected from the intravenous site prior to beginning the infusion. **Post-dose** (within 30 minutes of completion of the infusion) samples for intravenous study medication (LY3002813) should be collected from the arm that did not receive the infusion at V2 (Week 0), V5 (Week 12), V8 (Week 24), V15 (Week 52), and V20 (Week 72).

[rs] A single pre-dose LY3002813 sample should be collected before beginning the infusion at V3 (Week 4), V4 (Week 8), V6 (Week 16), V11 (Week 36), and V18 (Week 64). In addition, a single sample for serum LY3002813 should be collected at V21 (Week 76), or ED, and V801 (visits at which the patient may not receive a study drug infusion). If LY3002813 infusion is permanently discontinued but the patient remains in the study, one PK sample should be collected at the soonest scheduled visit regardless if serum LY3002813 is on the Schedule of Activities at that visit. Subsequent PK sample collection should follow the protocol Schedule of Activities for serum LY3002813 collection unless the scheduled visit exceeds 6 months since discontinuation of infusions. No additional serum collection for LY3002813 is required once the patient exceeds 6 months since discontinuation of LY3002813 infusions. Record the actual date and times of sample collection on the Lab Requisition Form.

~~[t] Prior to V3 (Week 4) and V6 (Week 16), a phone call should be made approximately 1 business day before the clinic visit to remind patients to hold the morning dose of oral study medication (LY3202626) on the day of the visit and to bring the dose to the clinic.~~

~~[u] Pre-dose (before taking oral study medication) and post-dose (prior to the patient departing the site) samples for oral study medication (LY3202626) should be collected at V3 (Week 4) and V6 (Week 16). Record the date and times of sample collection on the Lab Requisition Form. The actual time of LY3202626 dose administrations on the day of study visits will be recorded in the subject's case report form (CRF). In addition, the actual time of LY3202626 dose administration for the 2 days prior to each visit at which LY3202626 PK samples will be collected will be recorded in the subject's CRF.~~

~~[v] A single LY3202626 sample should be collected at V4 (Week 8), V5 (Week 12), V8 (Week 24), V11 (Week 36), V15 (Week 52), V18 (Week 64), and V21 (Week 76) or ED. Record the date and times of sample collection on the Lab Requisition Form. The actual time of LY3202626 dose administrations on the day of study visits will be recorded in the subject's CRF. If LY3202626 is permanently discontinued but the patient remains in the study, a final sample should be collected, provided the last dose of LY3202626 is within 3 days of the visit. No other PK samples for LY3202626 are required after the final sample. In addition, the actual time of LY3202626 dose administration for the 2 days prior to each visit at which LY3202626 PK samples will be collected will be recorded in the subject's CRF.~~

[sw] A blood sample will be collected to determine APOE genotype. The APOE genotype sample may be collected at an alternative visit if it cannot be collected at V2.

[tx] Blood for biomarker storage, and blood for pharmacogenomic samples are to be collected unless not allowed or unfeasible due to local regulations prohibiting sample transport outside of the country.

[uy] Pharmacogenomic samples may be collected at an alternative visit if they cannot be collected at V2. It will not be a protocol deviation~~violation~~ if a biomarker storage sample cannot be collected for technical reasons (e.g., if the site is unable to collect enough blood via venipuncture).

[vz] Sitting blood pressure and pulse will be measured after 5 minutes in the sitting position at **all** visits. Temperature will be collected with sitting vital signs.

~~w~~~~aa~~ In addition, orthostatic blood pressure and pulse will be measured at V2 (Week 0), V5 (Week 12), V8 (Week 24), V11 (Week 36), V15 (Week 52), V18 (Week 64), V21 (Week 76), ~~V22 (Week 80)~~ or ED, and at unscheduled visits after 5 minutes in the supine position and after 3 minutes standing.

~~x~~~~bb~~Electrocardiograms should be taken in triplicate at approximately 1-minute intervals. ECGs should be collected at approximately the same time of day, as much as possible, to minimize diurnal variation. ECGs are to be performed prior to the administration of intravenous study medication (LY3002813 and IV placebo).

~~y~~~~ee~~ If MRI is done on the same day as cognitive and functional assessments, then it should be done after cognitive and functional tests. MRI may be done before other visit procedures, including cognitive and functional tests, but in that case must be done at least 1 day before other visit procedures.

~~z~~~~dd~~The screening flortaucipir F18 PET scan, MRI, and florbetapir F18 PET scan done at V1 serve as the baseline flortaucipir F18 PET scan, MRI and florbetapir F18 PET scan, respectively.

~~aa~~~~ee~~ The V5 MRI is to be performed 2 weeks prior to the V5 (Week 12) LY3002813 infusion to allow for receipt and review of the central vendor MRI report prior to a possible LY3002813 dose change at V5 (Week 12).

~~bb~~~~ff~~ Females of childbearing potential are to have a urine pregnancy test (HCG) performed on the day of florbetapir F18 PET and flortaucipir F18 PET imaging before the florbetapir F18 dose or flortaucipir F18 dose is administered to confirm that they are not pregnant.

~~cc~~~~gg~~ All patients will have a flortaucipir F18 PET scan done at V21 (Week 76) or ED (if ED occurs more than 36 weeks after randomization) (see Appendix 5). Before the flortaucipir F18 PET scan, the investigator should review the patient's medical history and concomitant medications to verify there is no risk factor for ~~T~~torsades de ~~P~~pointes and review the most recent ECG. If clinically meaningful abnormalities are noted on the ECG, the advisability of the flortaucipir scan should be considered by the investigator in consultation with the Lilly-designated medical monitor. ~~Patients permanently discontinued from LY3202626 study treatment due to initiation of a prohibited medication known to prolong the QT interval should not have an ED flortaucipir scan unless the scan can be performed prior to initiation of the prohibited medication.~~ ***The study investigator and site clinical study team will not have access to the flortaucipir F18 follow-up scans, as the site clinical study team must remain blinded to any potential changes in tau deposition.***

~~dd~~~~hh~~ All patients will have double-blind period florbetapir F18 PET scans done at V8 (Week 24), V15 (Week 52), and V21 (Week 76) or ED (if ED occurs more than 8 weeks after a florbetapir F18 PET scan has been performed at a previous visit) (see Appendix 6). The study investigator and site clinical study team will not have access to any florbetapir F18 follow-up scans, as the site clinical study team must remain blinded to any potential changes in amyloid deposition.

~~cc~~~~ii~~Patients are to return to the site for an immunogenicity and safety follow-up visit (V~~isit~~801) at Week 88 (or 12 weeks after the ED visit) for collection of blood samples for anti-drug antibody (ADA) measurements and assessment of adverse events and concomitant medications. The need for additional study visits after V801 will be determined by results of the ADA sample taken at V801. A patient will stop immunogenicity follow-up visits when they either complete 3 additional quarterly visits (Week 100, Week 112, and Week 124) or complete a visit at which their ADA returns to baseline (2-fold titer from baseline), whichever occurs first. See Section 5.1.3 and Section 9.4.7.2 for details.

~~ff~~~~jj~~ Assessment is to include the audio voice recording of the rater's questions and the patient and caregiver responses to assessment questions.

3. Introduction

3.1. Study Rationale

~~This study evaluates use of two anti-amyloid therapies with different mechanisms of action targeting the amyloid cascade.~~ LY3002813 is an antibody directed at the pyroglutamate modification of the third amino acid of amyloid beta (N3pG Aβ) epitope that is present only in

brain amyloid plaques. It is being studied for the treatment of Alzheimer's disease (AD). The mechanism of action of LY3002813 is considered to be the targeting and removal of existing amyloid plaque, which is a key pathological hallmark of AD. The clinical strategy for LY3002813 targets the N3pG Aβ specific to amyloid plaque in the population of early symptomatic AD patients with existing brain amyloid load, as measured using the amyloid plaque biomarker, florbetapir F18 positron emission tomography (PET) imaging. ~~This LY3202626 is a synthetic small molecule, an inhibitor of β-site amyloid precursor protein (APP) cleaving enzyme [BACE]1, being assessed for the treatment of AD in an ongoing phase 2 study. The mechanism of action of LY3202626 is considered to be the reduction of Aβ monomer production through BACE 1 inhibition.~~ Combination therapy rationale is based on the amyloid hypothesis of AD, which states that the production and deposition of Aβ is an early and necessary event in the pathogenesis of AD (Selkoe 2000). Clinical support for this hypothesis comes from the demonstration that parenchymal Aβ levels are elevated before the appearance of symptoms of AD, and supported by genetic variants of AD that overproduce brain Aβ and genetic variants that protect against Aβ production (Jonsson et al. 2012; Fleisher et al. 2015). Furthermore, early in the disease, the presence of brain amyloid appears to increase the risk of conversion from mild cognitive impairment (MCI) to AD dementia (Doraiswamy et al. 2012). This suggests that enhanced clearance of Aβ will lead to slowing of AD progression.

~~This study, I5T-MC-AACG (AACG), is evaluating LY3002813, alone or in combination with LY3202626, compared with placebo. There is evidence suggesting that different forms of amyloid (monomeric, oligomeric and insoluble plaques) may all contribute to neurotoxicity independently (Selkoe 2008). Animal models suggest that treatment with a combination of a BACE inhibitor and an anti-plaque antibody will reduce soluble forms of amyloid and contribute to a greater reduction of deposited plaques compared with a plaque-specific antibody alone (Jacobsen et al. 2014). This may also provide synergistic effects on plaque removal compared to either drug given independently with more rapid and quantitatively greater amyloid removal (DeMattos 2016). Increased and more rapid removal of amyloid plaque plus removal of soluble forms of amyloid by parallel administration of both LY3002813 and LY3202626 over time is therefore hypothesized to have the potential for greater clinical efficacy than either drug given alone, with broader target engagement. Combination of therapeutics has been standard of care in most disease clinical practices, such as oncology, cardiology, and endocrinology. Of late there has been much discussion of the need for combination therapies in AD, as an ultimate path toward finding beneficial treatments for patients (Hendrix 2016).~~

Study I5T-MC-AACG (AACG) is a Phase 2, double-blind, placebo-controlled study to evaluate the safety and efficacy of N3pG antibody (LY3002813) ~~alone or in combination with BACE inhibitor (LY3202626)~~ in patients with early symptomatic AD (prodromal AD and mild dementia due to AD). Study AACG will assess whether removal of existing amyloid plaque ~~alone or in combination with lowering of Aβ production via BACE inhibition~~ can slow the progression of disease as assessed by clinical measures and biomarkers of disease pathology and neurodegeneration over up to 72 weeks of treatment~~76 weeks of treatment. No LY3202626 monotherapy arm is included in this proof of concept study. Clinical trials using LY3202626~~

~~and other BACE inhibitors as monotherapies are being conducted which may provide further understanding of the safety and efficacy data collected in this study.~~

Multiple biomarkers of disease progress will also be evaluated. The biomarker florbetapir F18 is a PET ligand that binds to fibrillar amyloid plaque. This biomarker can provide a qualitative and quantitative measurement of brain plaque load in patients with prodromal AD or mild AD dementia. The absence of significant florbetapir F18 signal on a visual read indicates that those patients clinically manifesting cognitive impairment have sparse to no amyloid plaques. As such, implementation of florbetapir F18 will provide a screening tool for entry into the clinical trial~~s~~ and provide a confirmation of amyloid pathology. Florbetapir F18 PET also provides quantitative assessment of fibrillar amyloid plaque in the brain and can assess amyloid plaque reductions from the brain by LY3002813 ~~and in combination with BACE inhibition with LY3202626~~.

3.2. Background

Alzheimer's disease is an age-related neurodegenerative disorder characterized by progressive decline in cognitive function and the ability to perform activities of daily living, ultimately resulting in dementia, typically with fatal complications. The amyloid hypothesis of AD postulates that the accumulation of amyloid-β peptide (Aβ) is an early and necessary event in the pathogenesis of AD. This hypothesis suggests that treatments that slow the accumulation of Aβ plaque in the brain or increase clearance of Aβ may be able to slow the progression of the AD clinical syndrome. ~~It is further postulated that combination of treatments that target both removal of Aβ plaque in the brain and reduce production of Aβ monomers may have added benefit.~~ The other hallmark neuropathological lesion of AD, intraneuronal neurofibrillary tangles consisting of tau proteins, is thought to be another marker for disease progression (Braak and Braak 1996). The relationship between these 2 pathologies is still unclear, although the presence of both is necessary for the diagnosis of definite AD.

~~Amyloid β is part of the APP, which is a transmembrane protein widely expressed on the cell surface, particularly in neurons. The APP has been found to be cleaved through 2 cleavage pathways involving 3 secretase enzymes: α-secretase, γ-secretase, and β-secretase (now called β-site APP-cleaving enzyme [BACE]1). Cleavage of APP by α-secretase precludes the formation of Aβ as the site is located within the Aβ sequence. In the second pathway, β-secretase cleaves the APP molecule, generating membrane-associated C99 and releasing a larger secreted fragment called secreted APP (sAPP)β. γ-Secretase then cleaves C99 in a heterogeneous fashion within the membrane releasing a variety of Aβ species that aggregate in protofibrils, then fibrils, which seem to comprise the mass of Aβ plaques in AD brain tissue (Turner et al. 2003). While both γ- and β-secretase inhibition represent effective means of precluding the formation of Aβ, β-secretase inhibition may provide improved safety and tolerability (Doody et al. 2013).~~

3.2.2. LY3002813 Phase 1 Studies

I5T-MC-AACD (Study AACD) is an ongoing ~~P~~phase 1b single- and multiple-dose study to assess the safety, tolerability, PK, and PD of single and multiple IV doses of LY3002813 in

patients with mild cognitive impairment due to AD or mild to moderate Alzheimer's dementia. It is evaluating~~currently enrolling, with~~ up to 150 patients in 6~~seven~~ different dosing cohorts receiving single, every 2 weeks, or every 4 weeks dosing of either 10 mg/kg, 20 mg/kg or 40 mg/kg of LY3002813. Treatment durations being assessed include single dose, six month dosing every two weeks, or up to 72 weeks of every 4 week dosing. Safety, PK and PD data from this ongoing study are used to inform further development of LY3002813. See Section 3.3 and the IB for detailed safety and PK information regarding LY3002813.

3.2.3. LY3202626 Nonclinical Studies

[Section deleted]

3.2.4. LY3202626 Clinical Studies

[Section deleted]

3.2.5. LY3002813/LY3202626 Combination Therapy - Nonclinical Findings

[Section deleted]

3.3. Benefit/Risk Assessment

3.3.1. Benefit

There is a large unmet medical need for disease-modifying treatments for AD. Data from the completed Phase 1a Study AACC ~~Animal models suggest that combination of a BACE inhibitor with an anti-plaque antibody will reduce soluble forms of amyloid~~ and from the ongoing Phase 1b Study AACD indicate a dramatic~~contribute to~~ reduction in cerebral amyloid (as assessed by florbetapir F18 PET imaging) in individuals who received repeated doses of at least 10 mg/kg (IB; Fleisher~~of insoluble plaques compared to a plaque-specific antibody alone. This may also provide synergistic effects on plaque removal compared to either drug given independently with more rapid and quantitatively greater amyloid removal (DeMattos 2016; Hole~~ et al. 2018). Along with ~~2016). Increased and more rapid removal of amyloid plaque plus removal of soluble forms of amyloid by parallel administration of both LY3002813 and LY3202626 over time is therefore hypothesized to have greater clinical efficacy than either drug given alone, with broader target engagement.~~

~~In addition to~~ assessment of safety and tolerability of LY3002813~~single and combined therapies~~, this study will assess whether removal of existing amyloid plaque ~~alone or in conjunction with inhibition of Aβ production in the brain~~ will show evidence of slowed clinical decline and change in biomarkers of disease progression relative to placebo treatment.

Although there are currently no available disease-modifying agents for the treatment of AD, there are several medications approved by the Food and Drug Administration (FDA) and Health Canada for the treatment of symptoms of AD; these include acetylcholinesterase inhibitors (e.g., donepezil, galantamine, and rivastigmine) and the N methyl D aspartate receptor antagonist memantine. Because these medications are considered standard of care for the treatment of AD,

participants in this trial will be permitted to take these medications during the course of the study, provided that they have been on a stable dose at the time of randomization and remain on a stable dose throughout the study.

3.3.2. Risks

Potential risks (discussed below) for LY3002813 ~~and LY3202626 given alone~~ include, but are not limited to~~:~~, ~~1) LY3002813 –~~ formation of anti-drug antibodies (ADA), hypersensitivity (immediate and non-immediate, including infusion-related reactions), and amyloid related imaging abnormalities (ARIA).~~) and 2) LY3202626 - hepatic effects, QT prolongation with overdose, skin or hair hypopigmentation, rash, retinal changes, and potential interactions with other drugs.~~

~~LY3002813 – Anti-Drug Antibodies:~~ High incidences of treatment-emergent anti-drug antibodies (TEADAs) have been observed in clinical studies with LY3002813. Although there were no serious adverse events (SAEs) related to the development of ADAs in Study AACC, the incidence of TEADAs in LY3002813-exposed patients and subjects was >90 %; in Study AACD, the incidence of TEADAs to date (final protocol) in LY3002813-exposed patients and subjects is approximately 75 %. In AACD, on 10 mg/kg Q2WK dosing, one patient was observed with a highly elevated ADA titer of 1:163840 on Day 144 postbaseline, with no clinical consequences. Anti-drug antibodies levels may affect PD levels of drug effect. Infusion reactions and ADAs are potential risks common to all large molecules. See the IB for details regarding TEADAs.

~~LY3002813 – Hypersensitivity (Immediate and Non-immediate), including infusion-related reactions)~~):

~~LY3002813 – Amyloid-Related Imaging Abnormalities~~:

~~LY3202626 - Hepatic effects~~: ~~In nonclinical studies, liver enzyme elevations were observed with LY3202626 in rats and dogs. These changes in the 1-month rat and dog studies occurred at exposures ≥245-fold the projected exposure at the high dose (12 mg) in the Phase 2 study. In the 6-month toxicology study in rats, mild alanine aminotransferase (ALT)/aspartate aminotransferase (AST) increases occurred in the high-dose group; these analytes remained increased at similar levels at the end of the 1-month recovery period, indicating lack of reversibility. In the 6-month rat study, ALT/AST increases did not occur at the mid-dose, and AUC-based margins at the mid-dose no-observed-adverse-effect level (NOAEL) of 4.5 mg/kg are 23- and 6-fold relative to the Phase 2 doses of 3 and 12 mg, respectively. No liver changes occurred in the 9-month toxicology study in dogs (AUC-based margin 39-fold relative to 12-mg dose in the Phase 2 study). Liver-related clinical chemistry analytes will be monitored in the clinical trial. In addition, the investigator may perform additional tests when clinically indicated. Clinical manifestations of hepatic injury may include fatigue, jaundice, steatosis, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or pruritus.~~

~~LY3202626 - QT Prolongation:~~ ~~Dose-dependent QT corrected for heart rate (QTc) prolongation (10 to 25 msec) occurred following repeated administration in dogs, at plasma unbound~~

~~maximum observed drug concentration (C_{max}) values approximately 3-fold of those projected for the highest planned Phase 2 clinical dose of 12 mg. Specific study exclusion criteria related to QTc are defined in the clinical protocol. Electrocardiograms and vital signs will be carefully monitored during the clinical trial. Cardiac signs and symptoms should be closely monitored in the presence of overdose.~~

~~***LY3202626 – Hypopigmentation*:** Dose-dependent decreased pigmentation of the skin and haircoat of dogs has been observed in preclinical studies with LY3202626. The lightening of haircoat and mucocutaneous junction epithelium did not impact the well-being of the dogs and was reversible during the treatment-free recovery period. Scheduled skin examinations will be performed by a dermatologist in the clinical trial, and are defined in the clinical protocol. If hypopigmentation is observed, patients may continue treatment. The location of hypopigmentation, occurrence of any associated cutaneous changes, and response after the treatment period should be monitored.~~

~~***LY3202626 – Retinal effects:*** Adverse retinal effects occurred in both the 1-month and 6-month toxicology studies with LY3202626 in rats, which included autofluorescent granule accumulation and hypertrophy of the retinal pigmented epithelium with photoreceptor degeneration. In the 6-month rat study, these retinal findings occurred only in the high-dose group (25 mg/kg) and did not reverse during the 1-month, treatment-free period. No retinal effects occurred at the NOAEL (4 mg/kg) in the 6-month rat toxicology study, providing area under the drug plasma concentration versus time curve (AUC)-based MOS of 23- and 6-fold to the Phase 2 doses of 3 and 12 mg. No adverse retinal changes occurred in dogs. Scheduled eye examinations by an ophthalmologist or optometrist (where permitted by law) will be performed in the clinical trial, and are defined in the clinical protocol. Patients who complain of vision disturbance during the clinical trial should be referred to the ophthalmologist or optometrist (where permitted by law) for unscheduled evaluation.~~

~~***LY3202626 – Potential Drug Interactions:*** LY3202626 has been shown to be a substrate of CYP3A and potentially a time-dependent inhibitor of CYP3A. Co-administration with a strong CYP3A inhibitor led to an approximate 20% increase in LY3202626 exposure, which is not thought to be clinically significant. The effect of LY3202626 on other CYP3A substrates is predicted to be modest. Accordingly, clinically meaningful drug interactions are not anticipated with LY3202626 administration. See the IB for a detailed assessment of clinical and nonclinical data regarding the potential for drug interactions.~~

3.3.3. Benefit/Risk Assessment Summary

To mitigate the potential risks described in Section 3.3.2, the current study will include standard safety assessments; i.e., reported AEs, clinical laboratory tests, immunogenicity assessments, vital sign and body weight measurements, 12-lead electrocardiograms (ECGs), and physical examinations.

Additional safety assessments will include neurological examinations (as part of each physical examination), ~~comprehensive eye examinations by an ophthalmologist or optometrist (where permitted by law), skin examinations by a dermatologist,~~ MRI examinations, and suicidality

evaluations using the Columbia-Suicide Severity Rating Scale (C SSRS). The current study will use an independent external Data Monitoring Committee (DMC) to monitor data on an ongoing basis to ensure the continuing safety of patients enrolled in this study.

The current study includes placebos ~~of both LY3002813 intravenously and LY3202626 orally~~ as a comparator, and approximately one-half~~third~~ of the patients will be randomized to placebo. In addition, all patients participating in the study will have a designated study partner who will have regular contact with the patient, accompany the patient to study visits, and liaise with the study staff between visits as needed (see Section 6.1 for additional information about the role of the study partner).

In conclusion, the available non-clinical and clinical data support the intravenous administration of LY3002813 ~~and the IV administration of LY3002813 in combination with the oral administration of LY3202626~~ to the intended study population according to the proposed clinical investigation plan and also provide a sufficient margin of safety for the proposed design and doses. There are currently no disease-modifying treatments for AD. The potential benefits of LY3002813 ~~and LY3002813 in combination with LY3202626~~ showing disease-modifying properties in AD are considered to outweigh the potential risks.

More information about the known and expected benefits, risks, SAEs and reasonably anticipated AEs of LY3002813 ~~and LY3202626~~ are to be found in the ~~respective~~ IB~~(s)~~.

4. Objectives and Endpoints

Table AACG.4.1. Objectives and Endpoints

Primary Objective	**Primary Endpoint**
To test the hypothesis that LY3002813 ~~alone and/or in combination with LY3202626~~ administered for up to 72~~76~~ weeks will decrease the cognitive and/or functional decline in patients with early symptomatic AD	Change in cognition and function as measured by the change in integrated Alzheimer's Disease Rating Scale (iADRS) score from baseline to 18 months
Secondary Objectives To assess the effect of LY3002813 ~~alone and in combination with LY3202626~~ vs. placebos on clinical progression in patients with early symptomatic AD	**Secondary Endpoints** Change in cognition from baseline to 18 months as measured by: • the change in Alzheimer's Disease Assessment Scale—Cognitive subscale (ADAS-Cog_{13}) score • the change in Clinical Dementia Rating Scale Sum of Boxes (CDR-SB) score • the change in Mini Mental State Examination (MMSE) score • the change in Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living scale (ADCS-iADL) score

To assess the effect of LY3002813 ~~alone and in combination with LY3202626~~ vs. placebo on brain amyloid deposition	Change in brain amyloid plaque deposition from baseline through 18 months as measured by florbetapir F18 PET scan
To assess the effect of LY3002813 ~~alone and in combination with LY3202626~~ vs. placebo on brain tau deposition	Change in brain tau deposition from baseline to 18 months as measured by flortaucipir F18 PET scan
To assess the effect of LY3002813 ~~alone and in combination with LY3202626~~ vs. placebo on brain volume measures	Change in volumetric MRI measures from baseline to 18 months.
~~To assess the effect of combination therapy with LY3002813 and LY3202626 vs LY3002813 alone on clinical progression in patients with early symptomatic AD~~	~~Change from baseline to 18 months in iADRS score, ADAS-Cog$_{13}$ score, CDR-SB score, MMSE score, ADCS-iADL score~~
Safety Objective	**Safety Endpoints**

To evaluate safety and tolerability of LY3002813 ~~alone and in combination with LY3202626~~	• Standard safety assessments:
	  o spontaneously reported adverse events (AEs)
	  o clinical laboratory tests
	  o vital sign and body weight measurements
	  o 12-lead ~~electrocardiograms (~~ECGs~~)~~
	  o physical and neurological examinations
	• MRI (ARIA and emergent radiological findings)
	• ~~Skin examination~~
	• ~~Eye examination~~
	• Columbia Suicide Severity Rating Scale (C-SSRS)

Exploratory Objectives	**Exploratory Endpoints**
To assess the effect of LY3002813 ~~alone and in combination with LY3202626~~ vs. placebo~~s, as well as combination therapy with LY3002813 and LY3202626 vs LY3002813 alone~~ on clinical progression in patients with early symptomatic AD	• the change in dependence level derived from ADCS-ADL scale scores
To assess peripheral PK and presence of anti-LY3002813 antibodies <u>over 72</u>~~in LY3002813 alone and in combination with LY3202626 over 76~~ weeks	• Plasma pharmacokinetics of LY3002813 • Anti-drug-antibodies (ADA) against LY3002813 including treatment-emergent ADA and neutralizing antibodies.
~~To assess peripheral PK of LY3202626 in combination with LY3002813 over 76 weeks~~	~~• Plasma Pharmacokinetics of LY3202626~~
~~To assess the effect of combination therapy with LY3002813 and LY3202626 vs LY3002813 alone on brain amyloid deposition~~	~~• Change in brain amyloid plaque deposition from baseline through 18 months as measured by florbetapir F18 PET scan~~

~~To assess the effect of combination therapy with LY3002813 and LY3202626 vs LY3002813 alone on brain tau deposition~~	• ~~Change in brain tau deposition from baseline to 18 months as measured by flortaucipir F18 PET scan~~

5. Study Design

5.1. Overall Design

Study AACG is a multicenter, randomized, double-blind, placebo-controlled, Phase 2 study of LY3002813~~, alone and in combination with LY3202626,~~ in subjects with early symptomatic AD. The 133~~124~~-week study includes a screening period of up to 9 weeks, a treatment period of up to 72~~76~~ weeks with final evaluations occurring 4 weeks later at Week 76, and ~~,~~ a 48~~4-week posttreatment follow-up, and a 44~~-week immunogenicity and safety follow-up period. Subjects who meet entry criteria will be randomized in a 1:1~~:1~~ ratio to one of the following treatments:

- LY3002813: ~~monotherapy (LY3002813-M):~~ IV LY3002813 (700 mg Q4WK for the first 3 doses, then 1400 mg Q4WK) for ~~in combination with daily oral placebo~~ up to 72~~76~~ weeks,

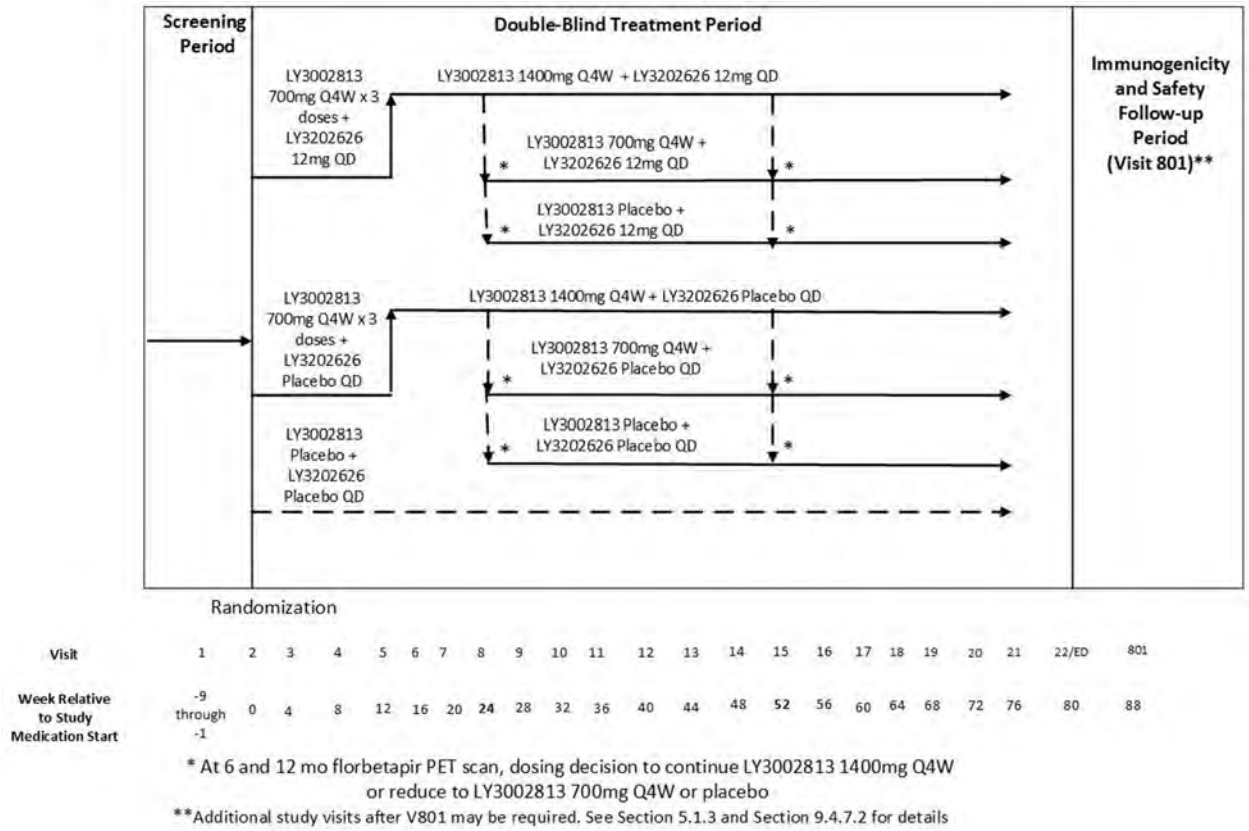
- ~~LY3002813 in combination with LY3202626 (LY3002813-C): IV LY3002813 (700 mg Q4WK for the first 3 doses, then 1400 mg Q4WK) in combination with daily oral LY3202626 (12 mg) up to 76 weeks,~~ or

- Placebo: IV placebo Q4WK ~~in combination with daily oral placebo~~ for up to 72~~76~~ weeks.

The primary hypothesis being tested is that LY3002813 administered ~~alone, or in combination with LY3202626,~~ for up to 72~~76~~ weeks will result in a significant slowing in cognitive/functional decline compared with placebo as measured by the change from baseline to the end of the double blind treatment period (Week 76) on the integrated Alzheimer's Disease Rating Scale (iADRS), in subjects with early symptomatic AD (where early symptomatic AD refers to the combination of 2 stages: prodromal AD [MCI -AD] and mild AD dementia; Alaka et al. 2015).

Under previous versions of this protocol, LY3002813 was administered in combination with LY3202626, an inhibitor of β site amyloid precursor protein cleaving enzyme (BACE)1. However, as of this amendment (d), the combination therapy and the oral placebo have been discontinued from the study.

[Old figure:]



* At 6 and 12 mo florbetapir PET scan, dosing decision to continue LY3002813 1400mg Q4W or reduce to LY3002813 700mg Q4W or placebo

**Additional study visits after V801 may be required. See Section 5.1.3 and Section 9.4.7.2 for details

[Updated figure:]

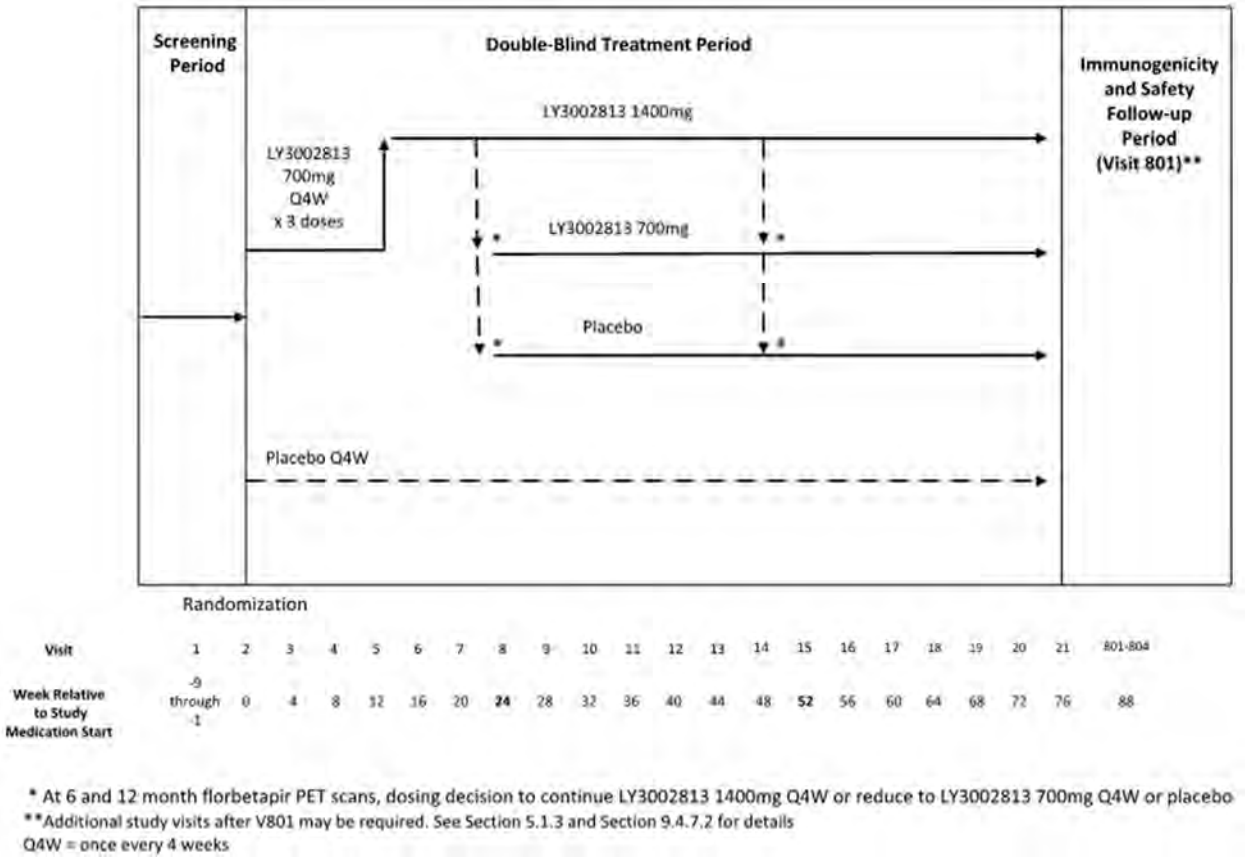


Figure AACG.5.1. Illustration of study design for Clinical Protocol I5T-MC-AACG.

5.1.1. Screening Period (Visit 1)

Once the MMSE criteria are met, 63 days are allowed for completion of Visit 1 screening assessments, procedures, and evaluation of results from laboratory tests, ECGs, physical and neurological examination, ~~ophthalmological and dermatological exams, f~~lortaucipir F18 PET, MRI, and florbetapir F18 PET. Even though florbetapir F18 PET imaging may be the last screening procedure of the study, it is expected that the centrally read florbetapir F18 PET results will be available within the timeframe of 63 days. However, it will not be a protocol deviation~~violation~~ should the screening florbetapir F18 PET results not be available until after 63 days.

Patients whose screening florbetapir F18 PET results are not available until after 63 days will remain eligible within Visit 1 until these results become available. **Note:** If a patient's screening florbetapir F18 PET results confirming evidence of amyloid burden are received by the site after 63 days, laboratory tests (blood hematology, chemistry, and serum human chorionic gonadotropin [HCG] for females of childbearing potential) are to be repeated for that patient. Results of the repeated labs are to be reviewed by the investigator or qualified designee for assessment of the patient's continued eligibility. Repeat screening for MMSE, CBB, C-SSRS,

ECG~~, ophthalmological and dermatological exams~~, flortaucipir F18 PET imaging, and MRI, and laboratory testing for hepatitis B surface antigen (HBsAg)~~,~~ and hepatitis C virus (HCV) RNA polymerase chain reaction (PCR), is not required.

Patients in active screening prior to implementation of amendment (d) remain eligible within Visit 1 until all screening procedures are completed and results are available. This will not be a protocol deviation. Patients who complete Visit 1 beyond 63 days are to repeat laboratory tests (blood hematology, chemistry, and serum HCG for females of childbearing potential) prior to being randomized. The results of these laboratory tests are to be reviewed by the investigator or qualified designee for assessment of the patient's continued eligibility. Repeat screening for MMSE, CBB, C-SSRS, ECG, flortaucipir F18 PET imaging, MRI, and laboratory testing for HBsAg and HCV RNA PCR is not required.

5.1.1.1. Screening Procedures

Screening entry and administrative procedures, cognitive assessments, safety assessments~~ (with the exception of ophthalmological and dermatological exams),~~ and laboratory assessments (see Schedule of Activities in Section 2) are to be done at Visit 1 before the screening flortaucipir F18 PET scan, MRI, and florbetapir F18 PET scan procedures.

5.1.1.1.1. Modified Hachinski Ischemic Scale (MHIS)

Patients who score ≥4 are more likely to have a dementia of vascular etiology and are excluded from participating in the trial.

5.1.1.1.2. Mini-Mental State Examination (MMSE)

The MMSE is a brief instrument used to assess cognitive function in ~~elderly~~ patients (Folstein et al.

5.1.1.1.5. Screening Ophthalmological and Dermatological Examinations

[Section deleted]

~~5.1.1.1.6.~~5.1.1.1.5. Screening Positron Emission Tomography and Magnetic Resonance Imaging

~~With the exception of ophthalmological and dermatological exams, a~~All other screening criteria should be met in order for the patient to proceed with flortaucipir F18 PET scan, followed by MRI, and a florbetapir F18 PET scan procedure.

~~5.1.1.1.6.2.~~5.1.1.1.5.2. Screening MRI

A local screening MRI will be performed at Visit 1 as part of the study eligibility criteria. With the exception of the evidence of amyloid pathology by florbetapir F18 PET scan, ~~and ophthalmological and dermatological exams,~~ a patient should meet all other Visit 1 eligibility criteria before having an MRI.

~~5.1.1.1.6.3.~~5.1.1.1.5.3. Screening Florbetapir F18 PET Scan

With the exception of the MRI ~~and ophthalmological and dermatological exams~~, a patient should meet all other Visit 1 eligibility criteria before having a screening florbetapir F18 PET scan.

5.1.2. Double-Blind Period (Visit 2 through Visit 21~~22~~)

Patients who meet entry criteria will be enrolled and randomized to receive up to 72~~76~~ weeks of treatment with LY3002813 ~~M, LY3002813 C, or placebo~~.

~~Patients are to take oral study medication (oral placebo or LY3202626) once per day in the morning. The first dose should be taken the morning after the first dispensing of oral study medication at Visit 2.~~

~~A final~~ Final endpoint measures and safety assessments ~~visit~~ for the double-blind period will be performed at Visit 21~~22~~ (Week 76~~80~~) 4 weeks following the patient's last dose of study medication.

5.1.3. Immunogenicity and Safety Follow-up Visits (Visits 801 through 804)

Patients are to return to the site for an immunogenicity and safety follow-up visits (Visit 801 through Visit 804) beginning at Week 88 (or 12 weeks after their last dose of LY3002813 for collection of blood samples for anti-drug antibody [~~(~~ADA; anti-LY3002813 antibody]) and PK measurement, ~~and~~ assessment of adverse events, C-SSRS, ~~and~~ concomitant medications, and vital signs.

5.2. Number of Participants

Approximately 266~~375~~ participants will be randomized.

5.4. Scientific Rationale for Study Design

Continuing Standard of Care. During the double-blind treatment period (V2 to V21~~V22~~), changes in doses of available symptomatic medications for MCI or AD will require reporting to the sponsor and these changes should occur only when necessary for the adequate overall care of the patient. The effect of LY3002813 treatment ~~alone or in combination with LY3202626~~ plus SOC will be compared with placebo plus SOC.

Dosing. As described more fully in Section 7.1, LY3002813 (700 mg or 1400 mg) will be administered every 4 weeks as an IV infusion of approximately 140 mL over a minimum of 30 minutes ~~and LY3202626 (12 mg) will be administered orally once a day~~.

Design. Study AACG is a multicenter, randomized, double-blind, placebo-controlled study of LY3002813~~, alone and in combination with LY3202626,~~ in patients with early symptomatic AD (where early symptomatic AD refers to the combination of 2 stages: prodromal AD [MCI AD] and mild AD dementia) (Alaka et al. 2015). The study is intended to characterize the benefits and risks of treatment with LY3002813 ~~alone or in combination with LY3202626~~ versus placebo in patients early symptomatic AD.

.... The use of a placebo comparator in Study AACG is needed to determine efficacy and safety of LY3002813 ~~monotherapy and LY3002813 combination~~ therapy.

The duration of the double-blind period of the study is 7680 weeks and includes up to 7276 weeks of treatment, with endpoint measures and safety assessments at the end of the double-blind treatment period (Week 76), to assess the safety, tolerability and efficacy of LY3002813 ~~alone or in combination with LY3202626~~ versus placebo~~, as well as LY3002813 alone versus LY3002813 in combination with LY3202626, and safety assessments at 80 weeks~~.

In addition to AE reporting, safety measures such as laboratory assessments, immunogenicity testing, vital signs and weight monitoring, ECG monitoring, physical examinations, neurological examinations ~~dermatological examinations, ophthalmological examinations,~~ MRI assessments, and assessments of suicidal ideation and behavior are included to facilitate a comprehensive safety evaluation. For patients enrolled under previous versions of this protocol, which included a combination arm of LY3002813 (N3pG) and LY3202626 (BACE inhibitor-IV), final dermatological examinations by a dermatologist and final comprehensive ophthalmological examinations by an ophthalmologist or optometrist (where permitted by law) will be performed at the next visit occurring after the patient stopped receiving LY3202626/oral placebo.

5.5. Justification for Dose

....

~~The LY3202626 dose of 12 mg administered orally once a day was selected based on current nonclinical pharmacology and toxicology data and clinical PK, PD and safety data. Doses of LY3202626 chosen for this study were based on central and peripheral PK/PD data from healthy subjects collected in a previous single- and multiple-dose study that were used to estimate the exposures necessary to achieve the desired levels of CSF Aβ reduction. These exposure targets were then used to select a daily dose of 12 mg LY3202626 for this study. This dose is less than the highest doses previously evaluated in healthy subjects (45 mg as a single dose, or 26 mg once a day for 14 days), which were found to be well tolerated. As described in Section 3.2.4, LY3202626 appears to be well tolerated in an ongoing Phase 2 study investigating the effect of 3 mg and 12 mg LY3202626. Together, these data suggest that a dose of 12 mg LY3202626 will be well tolerated in an AD population and will allow evaluation of near maximal inhibition of Aβ production.~~

6. Study Population

6.1. Inclusion Criteria

….

Patient/Subject Characteristics

[4] ....

A second study partner may serve as backup. The study partner(s) is/are required to accompany the patient for signing consent. One study partner is requested to be present on all days the ~~Columbia Suicide Severity Rating Scale (~~C-SSRS~~)~~/Self-Harm Supplement Form is administered and must be present on all days the~~and~~ cognitive and functional scales are administered (i.e., Visits 1, 2, 5, 8, 11, 15, 18, and 21/ED). If a patient has a

second study partner, it is preferred that one study partner be primarily responsible for the CDR and ADCS-ADL assessments. If a study partner(s) is not able to accompany the patient in person for visits other than those listed above, they must be available by telephone for the following assessments:

- AEs and concomitant medications
- relevant portions of the C-SSRS/Self-Harm Supplement Forms
- ~~CDR and ADCS-ADL (primary study partner if possible)~~

6.2. Exclusion Criteria

Medical Conditions

[11] Current serious or unstable illnesses including ~~retinal,~~ cardiovascular, hepatic, renal, gastroenterologic, respiratory, endocrinologic, neurologic (other than AD), psychiatric, immunologic, or hematologic disease and other conditions that, in the investigator's opinion, could interfere with the analyses in this study; or has a life expectancy of <24 months.

[57] [Note: Criterion #57 has been deleted.] ~~Ocular pathology that significantly limits ability to reliably evaluate vision or the retina, or puts participant at undue risk for vision loss during the study.~~

[18] [Note: Criterion #18 has been deleted.] ~~History of vitiligo and/or current evidence of post-inflammatory hypopigmentation.~~

Magnetic Resonance Imaging, Vital Signs, Electrocardiograms, Laboratory Tests, and Physical Examination

[54] Patients with past history of Hepatitis C should have ~~hepatitis C virus (~~HCV~~)~~ ~~ribonucleic acid (~~RNA~~)~~ ~~polymerase chain reaction (~~PCR~~)~~ testing at screening and are excluded if HCV RNA PCR is positive.

Prior/Concomitant Therapy

[32] [Note: Criterion #32 has been deleted.] ~~Current use of strong inducers of CYP3A (see the Manual of Operations for a list of excluded drugs).~~

[37] [Note: Criterion #37 has been deleted.] ~~Have known allergies to LY3202626, related compounds, or any components of the formulation.~~

Prior/Concurrent Clinical Trial Experience

[47] [Note: Criterion #47 has been replaced by criterion~~a~~ #55 ~~and #56~~.]

[56] [Note: Criterion #56 has been deleted.] ~~Have previously had LY3202626 treatment discontinued due to treatment-related adverse event.~~

6.2.1. Rationale for Exclusion of Certain Study Candidates

The use of LY3002813 ~~and LY3202626~~ in older patients is anticipated; thus this study will specifically examine the efficacy and safety in an elderly population. Criterion [2] defines the population age range for the purposes of this study. Therefore, patients not meeting the age criterion are excluded.

6.3. Lifestyle Restrictions

~~2. Patients should avoid use of tanning beds and self-tanning products.~~

~~3. Patients should wear a hat and appropriate clothing when exposed to sunlight; use a sunscreen with a skin protection factor (SPF) of at least 15; and protect their lips with a lip balm containing sunblock.~~

7. Treatments

7.1. Treatments Administered

This study involves a comparison of LY3002813 administered as an IV infusion of approximately 140 mL over a minimum of 30 minutes compared ~~with LY3002813 in combination with LY3202626 administered orally once a day, and~~ placebo. In the double-blind period, the treatment groups will be given ~~either~~ an IV infusion of LY3002813 ~~monotherapy (LY3002813-M), LY3002813 combination therapy (LY3002813-C),~~ or Placebo for up to 72~~76~~ weeks.

....

~~The LY3202626 dose will remain 12 mg throughout the double-blind treatment period.~~ Table AACG.7.1 shows the 2~~3~~ treatment regimens during the double-blind period.

Table AACG.7.1. Treatment Regimens, Double-Blind Period

Regimen	Dose Visit 2 (Week 0) through Visit 21 (Week 76)
~~LY3002813-M~~	~~LY3002813 (700 mg intravenous infusion every 4 weeks x 3 doses, then 1400 mg intravenous infusion every 4 weeks for up to 72 weeks) in combination with orally dosed placebo tablet once per day in the morning x 76 weeks~~
LY3002813-~~C~~	LY3002813 (700 mg intravenous infusion every 4 weeks x 3 doses, then 1400 mg intravenous infusion every 4 weeks for up to 72 weeks) ~~in combination with LY3202626 (12 mg tablet orally once a day in the morning for 76 weeks)~~
Placebo	Intravenously dosed placebo infusion every 4 weeks for up to 72 weeks ~~in combination with orally dosed placebo tablet once per day in the morning x 76 weeks~~

~~Abbreviations: C = combination therapy; M = monotherapy.~~

~~7.1.1.2. LY3202626 Packaging and Labelling~~

~~LY3202626 will be supplied as 12-mg tablets. The study drug and placebo will be identical in appearance and will be packaged in blister packs.~~

7.2. Method of Treatment Assignment

Patients will be randomized to LY3002813~~-M, LY3002813-C,~~ or Placebo in a 1:1~~:1~~ ratio.

7.2.1. Selection and Timing of Doses

Assessment of LY3002813 ~~and LY3202626~~ safety and tolerability is a central objective; therefore, monitoring 100 patients on LY3002813~~-M~~ over 72~~76~~ weeks ~~in parallel with approximately 100 patients on LY3002813-C over 76 weeks of exposure~~ provides data to assess safety for further clinical development.

The actual time of ~~both~~ LY3002813 ~~and LY3202626~~ dose administration~~s~~ on the day of study visits will be recorded in the subject's case report form (CRF). ~~In addition, the actual time of LY3202626 dose administration for the 2 days prior to each visit at which LY3202626 PK samples will be collected will be recorded in the subject's CRF.~~

7.2.1.1. LY3002813: Selection and Timing of Doses

.... Intravenous study medication given at a dosing interval of less than 21 days at any time during the study will be considered a protocol deviation~~violation~~.

7.2.1.2. LY3202626: Selection and Timing of Doses

[Section deleted]

7.3. Blinding

This is a double-blind study, with design to maintain blinding to treatment~~both LY3002813 and LY3202626 treatments~~.

7.4. Dosage Modification

7.4.1. LY3002813 Dosage Modification for ARIA-E

~~7.4.1.1. LY3002813 Dosage Modification for ARIA-E~~

~~Patients will continue LY3202626 at 12 mg per day.~~

~~7.4.1.2.~~ 7.4.2 LY3002813 Dosage Modification for ARIA-H

~~Patients will continue LY3202626 at 12 mg per day.~~

~~Patients permanently discontinued from LY3002813 are to continue taking LY3202626 unless they are permanently discontinued from LY3202626 treatment or from the trial.~~

7.4.2. LY3202626 Dosage Modification

[Section deleted]

7.6.2. LY3202626 Treatment Compliance

[Section deleted]

7.7. Concomitant Therapy

Allowed Medications. Use of approved or standard of care treatments for AD is permitted during the study, provided that such medications dose has been unchanged for 2 months before Visit 2. Doses of these medications should remain constant throughout the double-blind period (Visit 2 to Visit 21~~22~~).

Prior to V21~~V22~~, before a patient starts, stops, or changes doses of AChEIs and/or memantine or other treatments for their AD, the Sponsor or designee must be contacted to determine whether or not the patient should continue in the study and whether or not clinical outcome measures should be performed. Failure to notify Lilly or its designee regarding starting, stopping or changing doses of AChEIs and/or memantine or other treatments for their AD prior to V21~~V22~~ will be considered a protocol deviation~~violation~~.

If unforeseen starting, stopping, or changing of stable doses of drugs affecting CNS function occurs prior to ***V21~~V22~~*** of the study, Lilly or its designee must be contacted to determine whether or not the patient should continue in the study and whether or not outcome measures should be performed. ***Failure to notify Lilly or its designee regarding starting, stopping or changing doses of CNS medications prior to V21~~V22~~ of the study will be considered a protocol deviation~~violation~~.***

Excluded Medications.

~~Concomitant therapies that are prohibited during treatment with LY3002813:~~ IgG therapy (also known as gamma globulin or intravenous immunoglobulin [IVIG]) is not allowed during the study.

~~Concomitant therapies that are prohibited during treatment with LY3202626:~~

- ~~Use of depigmenting agents, such as, hydroquinone~~
- ~~Current use of strong inducers of CYP3A (See the Manual of Operations for a list of excluded drugs)~~
- ~~Current use of drugs known to significantly prolong the QT interval (See the Manual of Operations for a list of excluded drugs)~~
- ~~Use of any drug of abuse, including but not limited to cannabis, illicit amphetamine, cocaine, illicit opiates, propoxyphene, methadone, methaqualone, phencyclidine, or illicit barbiturate~~

7.8. Treatment after the End of the Study

7.8.1. Treatment after Study Completion

There is no planned open label extension at this time, or plan to otherwise make LY3002813 ~~or LY3202626~~ available to patients after conclusion of the study.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

- Treatment with LY3002813 will also be permanently discontinued in patients with:
  - Adverse event or clinically significant laboratory value, ECG result, physical examination finding, ~~(including eye or skin examination),~~ MRI finding (such as symptomatic ischemic stroke), C -SSRS result, or vital sign measurement of such severity that, in the opinion of the investigator or Lilly-designated medical monitor, continued treatment is not in the best interest of the patient.

Patients ~~permanently discontinued from one treatment~~ may ~~continue to receive the other treatment and continue in the trial. Patients may also~~ permanently discontinue study treatment~~both treatments~~ and remain in the trial.

~~If LY3202626 oral dose is permanently discontinued but the patient remains in the study, a final sample should be collected, provided the last dose of LY3202626 is within 3 days of the visit. Dosing dates and times should be collected. No other PK samples for LY3202626 are required after the final sample.~~

8.1.1. Temporary Discontinuation from Study Treatment

8.1.1.1. Temporary Discontinuation from LY3002813 Study Treatment Due to ARIA-E

~~8.1.1.1.1. Temporary Discontinuation from LY3002813 Study Treatment Due to ARIA-E~~

8.1.1.2. Temporary Discontinuation from LY3202626 Study Treatment

[Section deleted]

8.2. Discontinuation from the Study

Subjects discontinuing from the study prematurely for any reason must complete AE and other safety follow-up per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol. In addition, subjects discontinuing from the study prematurely should be encouraged to return to the site beginning 12 weeks after their ED visit for ~~an~~ immunogenicity and safety assessments (Visits~~assessment visit (Visit~~ 801 through 804, as described in Section 5.1.3).

9. Study Assessments and Procedures

9.1. Efficacy Assessments

Note that the ADAS-Cog and MMSE ~~should~~ must be administered by a different rater than the ADCS-ADL and CDR.

9.1.2. Secondary Efficacy Assessments

9.1.2.4. Mini-Mental State Examination (MMSE)

The MMSE is a brief instrument used to assess cognitive function in ~~elderly~~ patients (Folstein et al. 1975).

9.1.3. Biomarker Efficacy Measures (Double-Blind Period)

Florbetapir F18 PET scan. Change in amyloid burden (as assessed by florbetapir F18 PET signal) will be compared in LY3002813-~~, LY3002813/LY3202626~~ and placebo-treated patients for those patients who undergo florbetapir F18 PET scans at baseline, Week 52 [Visit 15], and Week 76 [Visit 21] or ~~early discontinuation [~~ED~~]~~) as described in the Schedule of Activities (Section 2).

Flortaucipir F18 PET scan. Change in tau burden (as assessed by flortaucipir F18 PET signal) will be compared in LY3002813-~~, LY3002813/LY3202626~~ and placebo-treated patients for those patients who undergo both baseline and endpoint (Visit 21 [Week 76] or ED) flortaucipir F18 scans as described in the Schedule of Activities (Section 2).

Volumetric MRI. Magnetic resonance imaging of the brain will be performed according to the Schedule of Activities (Section 2). LY3002813-~~, LY3002813/LY3202626~~ and placebo-treatment effects on volumetric MRI will be assessed and compared to evaluate the loss of brain volume that occurs in AD patients.

9.2.1.2. Adverse Events of Special Interest

Specific safety topics of interest for this study include, but are not limited to, the following:

- ~~QT prolongation~~
- ~~Adverse eye effects~~
- ~~Adverse skin effects including rash and hypopigmentation~~
- ~~Liver toxicity~~

9.3. Treatment of Overdose

~~*9.3.1. Treatment of LY3002813 Overdose*~~

There is no known antidote to LY3002813. In case of overdose, use appropriate monitoring and supportive therapy.

~~*9.3.2. Treatment of LY3202626 Overdose*~~

~~There is no known antidote to LY3202626. In the case of known or suspected overdose, monitoring of cardiac, hepatic, and hematological effects is essential, and appropriate supportive therapy should be initiated, as appropriate. Refer to the LY3202626 IB.~~

9.4. Safety

9.4.1 Physical and Neurological Examinations

Complete physical examinations will be performed at screening, baseline, and Weeks 12, 24, 52, 76, ~~80,~~ and ED as indicated in the Schedule of Activities (Section 2).

9.4.6 Other Tests

9.4.6.3. Ophthalmological Examination

While the BACE inhibitor LY3202626 is no longer being administered in this study (see Section 5.1), ophthalmological examinations in patients who previously received LY3202626 or oral placebo will be performed at the next scheduled examination time point after their final dose of oral study medication (see the Schedule of Activities [Section 2]). Patients who received LY3202626/oral placebo after their Visit 9 ophthalmological examination are to have an unscheduled ophthalmological examination at the next available opportunity. Patients screened or randomized under the current amendment are not required to undergo any ophthalmological examinations at baseline or any other study visits.

~~All~~ Patients who previously received LY3202626 or oral placebo will undergo comprehensive ophthalmological examinations performed by an ophthalmologist or optometrist (where permitted by law) to assess visual function and morphology. Scheduled examinations will include the following: visual acuity, intraocular pressure, dilated funduscopic exam (dilation only performed in patients without contraindication to mydriatics), slit lamp exam, color photography of the retina, and optical coherence tomography (OCT) or equivalent; examinations will also include color vision assessment. Assessments will preferably be performed ~~at times shown in the Schedule of Activities (Section 2), preferably~~ by the same ophthalmologist or optometrist for each patient's visit. Patients who complain of vision disturbance, such as change in field of vision, color, acuity or anything potentially localizable to the retina, during the clinical trial should be referred to the ophthalmologist or optometrist (where permitted by law) for unscheduled evaluation.

Data from the ~~eye~~ ophthalmological examination visits will be provided from the local ophthalmologist or optometrist to the investigator. ~~Based on the morphological and functional results, the investigator will include or exclude the patient in consultation with the performing eye examiner,.~~

The local ophthalmologist or optometrist will review the color photography and OCT to aid in ~~the investigator's assessment of study eligibility and for~~ immediate patient management. Additionally, the color photography of retina and OCT will be analyzed by a central reader.

9.4.6.4. Dermatological Examination

While the BACE inhibitor LY3202626 is no longer being administered in this study, ~~A~~ complete dermatological examinations in patients who previously received LY3202626 or oral placebo will ~~skin examination will~~ be performed at the next scheduled examination time point after their final dose of oral study medication (see ~~times shown in~~ the Schedule of Activities ~~(~~[Section 2]). Patients who received LY3202626/oral placebo after their Visit 8 dermatological examination

are to have an unscheduled dermatological examination at the next available opportunity. Patients screened or randomized under the current amendment are not required to undergo any skin exams at baseline or any other study visits.

This examination will ~~),~~ preferably be performed by the same dermatologist for each patient's visit. All ~~skin~~ dermatological examinations must be performed by a dermatologist who will inspect the patient's unclothed full body using an ultraviolet (UV) light. The initial examination will include Fitzpatrick skin-type classification scale.

9.4.7. Safety Monitoring

The Lilly clinical research physician or scientist will, as appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist, and periodically review:

- AEs including monitoring of hypersensitivity and infusion reactions, AEs associated with anti-LY3002813 antibodies (immunogenicity), ARIA-H, ARIA-E ~~-E~~, ~~eye and skin,~~ ECG findings, neurological findings, hemorrhagic stroke, microhemorrhage (cerebral microhemorrhage, cerebellar microhemorrhage, brain stem microhemorrhage) as identified by investigator, and suicide-related thoughts and behaviors.

9.4.7.1.2. Management of Infusion Reactions

Additional data should also be collected via the CRF/electronic data entry. P~~p~~lease see the Operations Manual for more detail.

9.4.7.2. LY3002813 Immunogenicity

In order to preserve the blind, patients will need to complete Visits 801 through~~to~~ 804 until all patients in the trial have reached Visit 21~~22~~ and datalock for the treatment period has been achieved.

In the event of a finding of hypersensitivity, the investigator is to complete the CRF regarding the presence or absence of symptoms related to the hypersensitivity.

9.4.7.4. Amyloid-Related Imaging Abnormalities (ARIA-E and ARIA-H)

In the event of a finding of ARIA E on MRI, the investigator is to complete the CRF regarding the presence or absence of symptoms related to the ARIA-E.

If the above mentioned symptoms are reported, and ARIA E is suspected, then the abnormality is best detected by fluid attenuation inversion recovery (FLAIR) sequences on ~~magnetic resonance imaging (~~MRI~~)~~ and ARIA H is best detected with the T2* gradient recalled echo on MRI.

9.4.8. Appropriateness of Safety Assessments

The clinical safety measurements (AE reporting, physical examinations, neurological examinations, ~~ophthalmological examinations, dermatological examinations,~~ vital signs, ECGs, and clinical safety laboratory tests [including immunogenicity]; Section 9.2 and Section 9.4) are

well-established methods in drug development research and are standard procedures for clinical trials.

Performance of ophthalmological and dermatological examinations is~~are~~ indicated in subjects who were previously treated with LY3202626, based on the potential for the occurrence of adverse retinal effects and hypopigmentation, respectively, during treatment with LY3202626. While LY3202626 is no longer being administered in this study, dermatological and ophthalmological examinations in subjects who previously received this therapy or oral placebo will be performed at the next scheduled examination time point after their final dose of oral study medication, in accordance with the Schedule of Activities (Section 2). Patients who received LY3202626/oral placebo after their Visit 8 or 9 dermatological or ophthalmological examination are to have an unscheduled examination at the next available opportunity. Patients screened or randomized under the current amendment are not required to undergo any dermatological or ophthalmological examinations at baseline or any other study visits.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 4 mL each will be collected to determine the serum concentrations of LY3002813 ~~and venous blood samples of approximately 2 mL each will be collected to determine plasma concentrations of LY3202626~~. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

~~If LY3202626 oral dose is permanently discontinued but the patient remains in the study, a final sample should be collected, provided the last dose of LY3202626 is within 3 days of the visit. Dosing dates and times should be collected. No other PK samples for LY3202626 are required after the final sample.~~

9.7. Pharmacogenomics [OR] Genetics

9.7.1. Apolipoprotein E Genotyping

Blood sampling for APOE genotyping will be performed as shown in the ~~in the~~ Schedule of Activities (Section 2).

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 250~~375~~ subjects will be enrolled and randomized in a 1:1~~:1~~ ratio to the 2~~three~~ treatment arms (placebo~~, LY3002813-M,~~ and LY3002813-~~C~~). It is expected that approximately 200~~300~~ subjects will complete the double-blind treatment period of the study (approximately 100 per treatment arm). This sample size will provide approximately 84~~86~~% power to demonstrate that the~~at least one~~ active treatment arm has a ≥ 0.6 posterior probability of slowing down iADRS progression over placebo by at least 3 points. The assumption for power calculation is that mean progression levels in the placebo~~, LY3002813-M~~ and LY3002813-~~C~~ arms are approximately 12~~, 8 (33% slowing),~~ and 6 points (50% slowing) over 18 months, respectively,

with common standard deviation of 17. If the~~both~~ active treatment arm is~~arms are~~ placebo-like with no efficacy, the probability of passing the efficacy criterion specified above (i.e., false positive) is approximately 6~~11~~%. The simulation for the power calculation and sample size determination was carried out in FACTS Version 6.0~~5.5~~.

10.2. Populations for Analyses

For purposes of analysis, in general the following populations are defined unless otherwise specified:

For efficacy analysis, the Full Analysis Set will group patients according to randomized treatment assignment (LY3002813 or placebo), even if the patient does not take the assigned treatment, does not receive the correct treatment, or otherwise does not follow the protocol. When change from baseline is assessed, patients will be included in the analysis only if both a baseline and at least 1 valid post-baseline measure are available.

For safety analysis, all patients who received at least 1 dose of randomized study treatment (LY3002813~~, LY3202626~~ or placebo) will be included in the safety analysis set. In safety data presentations, erroneously treated patients (e.g., those randomized to "Treatment A" but actually given "Treatment B") will be accounted for in their actual treatment groups.

There were approximately 48 patients randomized before the removal of LY3202626 treatment in protocol amendment (d) (about 16 each in the LY3002813 and LY3202626 combination therapy arm, LY3002813 monotherapy arm, and placebo arm). Patients already randomized to the former LY3002813 monotherapy arm and placebo arm will be pooled with patients randomized after protocol amendment (d) to form the Full Analysis Set and safety analysis set specified above. Data from patients randomized to the LY3002813 and LY3202626 combination therapy arm will be summarized separately and will not be included in treatment comparisons on efficacy and safety endpoints. The total number of patients to be randomized in the study is approximately 266.

10.3.2. Treatment Group Comparability

10.3.2.2. Subject Characteristics

The patient's age, gender, race, height, body weight, BMI (weight (kg) / [height (m)]2), tobacco use, alcohol use, caffeine use, years of education, work status, time since onset of first AD symptoms, time since diagnosis, baseline MMSE, CBB score at Visit 1, apolipoprotein E (APOE) genotype (E4 carrier vs. non-carrier), having 1 or more first degree relatives with AD, and AChEI and/or memantine use at baseline will be recorded.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary objective of this study is to test the hypothesis that IV infusion of LY3002813 ~~alone or in combination with LY3202626~~ will slow the cognitive and/or functional decline of AD as

measured by the composite measure iADRS compared with placebo in patients with early symptomatic AD. This will be assessed using an MMRM analysis.

The primary time point for treatment comparison will be at Week 76. The treatment group contrast in least-squares mean progression and its associated p-value and 95% CI will be calculated for the treatment comparison~~s~~ of LY3002813 ~~-M~~ vs. placebo ~~and LY3002813-C vs. placebo,~~ using the MMRM model specified above. In addition, Bayesian posterior probability of the active treatment arm being superior to placebo by at least a margin of interest (25% slowing of placebo progression) will also be calculated assuming a non-informative prior.

10.3.4. Safety Analyses

10.3.4.5. ARIA-E and ARIA-H

The incidence of ARIA-E will be summarized. Change in ARIA-E status from baseline, to each subsequent MRI (in the event of unscheduled MRIs), and to double-blind period endpoint (Visit 21~~22~~) will be compared between treatment groups using Fisher's exact test.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Compartmental modeling of LY3002813 ~~and LY3202626~~ PK data using nonlinear mixed effects modeling or other appropriate software may be explored, and population estimates for clearance and central volume of distribution may be reported. Depending on the model selected, other PK parameters may also be reported. Exploratory graphical analyses of the effect of dose level or demographic factors on PK parameters may be conducted. If appropriate, data from other studies of LY3002813 ~~or LY3202626~~ may ~~in~~ be used in this analysis.

Concentrations of LY3202626 were collected under the original version of this protocol, as well as amendments (a-c). These data will be summarized in the final study report and may be analyzed graphically. If appropriate, exploratory analyses may be conducted to evaluate potential relationships between LY3202626 concentrations and LY3002813 concentration.

The PK/PD relationships between plasma LY3002813 concentration and SUVr, cognitive endpoints, ARIA incidence rate or other markers of PD activity may be explored graphically. The relationship between the presence of antibodies to LY3002813 and PK, PD, safety and/or efficacy may be assessed graphically. ~~The effect of LY3202626 exposure on SUVr, cognitive endpoints, or other markers of PD activity may also be explored graphically. Graphical and/or descriptive analyses may be explored to evaluate potential interactions between LY3002813 and LY3202626 for PK. If warranted, additional analysis may be explored to evaluate potential interactions for ADA, PD and other endpoints (PET scan, ARIA-E, etc.).~~

10.3.6. Interim Analyses

There will be periodic~~al~~ safety data reviews during the study and the external DMC is authorized to evaluate results from unblinded safety data reviews.

11. References

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Appendix 5. Flortaucipir F18 Tau PET Imaging

Inclusion Criteria for Flortaucipir F18 PET Scans

With the exception of the ~~ophthalmological and dermatological examinations,~~ MRI and florbetapir F18 PET scan, a patient should meet all other Visit 1 eligibility criteria before having a flortaucipir F18 PET scan.

PET Scan-Specific Information

PET Scan Procedures

Scan Safety

The primary risk related to flortaucipir F18 PET is F18's radiation exposure.

....

- flortaucipir F18 PET scans should ~~to~~ be performed at least 16 hours apart from the florbetapir F18 PET scans due to the half-life of fluorine 18.

With respect to other compound-related risks, flortaucipir~~AV-1451~~ was positive in the in vitro hERG assay.

Nonperformance of postbaseline flortaucipir F18 PET scans in patients taking a medication known to prolong QT interval will not be considered a protocol ~~deviation~~violation.

Appendix 6. Florbetapir F18 Amyloid PET Imaging

Inclusion Criteria for Florbetapir F18 PET Scans

With the exception of the MRI, ~~ophthalmological and dermatological exams,~~ a patient should meet all other Visit 1 eligibility criteria before having a florbetapir F18 PET scan.

PET Scan-Specific Information

PET Scan Procedures

PET Scan Safety

- florbetapir F18 PET scans should ~~to~~ be performed at least 16 hours apart from the ~~18F~~ flortaucipir F18 PET scan due to the half-life of fluorine 18.

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