Official Protocol Title:	A Parallel-Group, Double Blind Long Term Safety Trial of MK-8931 in Subjects with Alzheimer's Disease. (Protocol No. MK-8931-017-21) (also known as SCH 900931, P07738)
NCT number:	NCT01739348
Document Date:	01-AUG-2016

1.0 TITLE PAGE

Abbreviated Title	A Long Term Safety Trial of MK-8931 in AD (EPOCH)
Title	A Parallel-Group, Double Blind Long Term Safety Trial of MK-8931 in Subjects with Alzheimer's Disease. (Protocol No. MK-8931-017-21) (also known as SCH 900931, P07738)
Sponsor	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Sponsor's Address	One Merck Drive P.O. Box 100 Whitehouse Station, NJ 08889-0100, U.S.A.
IND No.	110,186
EudraCT No.	2015-000616-18
Trial Physician/Director	PPD
Phase	2/3
Date of Finalization of This Current Version of the Protocol	**01-AUG-2016** – Amendment 017-21 (France Specific **)**
Previous Versions of the Protocol	**26-JUL-2016**– Amendment No.20 (Country Specific) **22-JUL-2016**– Amendment No.19 (France Specific) **21-JUL-2016**– Amendment No.18 (Country Specific) **28-JUN-2016** – Amendment No.17 **11-Sep-2015 –** Amendment 017-16 (France Specific) **26 JUN 2015** – Amendment 017-15 France Specific **24 APR 2015 - Amendment 017-14 Country Specific** **09 APR 2015 - Amendment 017-13** **05 MAR 2015**– Amendment 017-12 Country Specific **26 FEB 2015 -** Amendment 017-11 Country Specific **18 DEC 2014 -** Amendment 017-10 **08 AUG 2014 -** Amendment 017-09 Country Specific **11 FEB 2014 -** Amendment #5 (017-08) **14 AUG 2013 -** Amendment #4 (017-07) **08 NOV 2012 -** Amendment #3 Brazil Version 1 (017-06) **26 SEP 2012 -** Amendment #3 (017-05) **23 JUL 2012 -** Amendment #2 Brazil Version 2 (017-04) **23 JUL 2012 -** Amendment #2 Brazil Version 1 (017-03) **20 JUN 2012 -** Amendment #2 (017-02) **31 MAY 2012 -** Amendment #1 (017-01) **19 JAN 2012 -** Initial Protocol (017-00)
Protocol Template Approval Date	28 MAR 2012

C O N F I D E N T I A L
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This protocol amendment is applicable only to France.

SUMMARY OF CHANGES

PRIMARY REASON FOR THIS AMENDMENT:

This study (PN017-21) is a long term safety extension of the base protocol, PN017-19 for use in locations that require separate documents. For locations that do not require separate documents, protocol PN017-17 is used, which includes the base protocol and the extension in one protocol.

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
2.2 7.1 7.6	Trial Flow Chart Overall Trial Design Trial Procedures	Added pharmacokinetic (PK) visits at weeks 4 and 13 of the extension (ie, weeks 82 and 91 from randomization visit in main study) Added PK sample collection to trial procedures.	Added two PK collections to this extension protocol to facilitate robust PK and PK/PD modeling for the MK-8931 program. In the base protocol, both plasma and dried blood spot (DBS) samples were collected initially for assessment of PK, but plasma sampling was dropped when preliminary analyses indicated that DBS samples were sufficient. However, due to quality issues identified with some DBS samples in the base protocol; dual sample collection (plasma and DBS) is being reinstated for the PN017 protocols. These two additional PK time points are being added to offset some of the collected DBS samples with quality issues.
2.0	Synopsis	Added note that Sponsor will be unblinded following the completion of the initial 78-week trial but some Sponsor	Maintaining Sponsor blinding for efficacy data collected at 24 months in the long-term trial is needed to support the

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
5.3	Trial Design Rationale	personnel will remain blinded during the long-term trial, as necessary, to support the conduct of the trial and the collection of efficacy data.	primary efficacy objective for the long-term trial

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
2.2	Trial Flow Chart for Long Term Safety Trial	Added the following to footnote 'j' for dermatology: "or who have >6 month gap in study therapy between Visit 10 and 10B".	Text in footnote was inadvertently missed out from previous amendment
2.2	Trial Flow Chart for Long Term Safety Trial	Added the following text to footnote "b" in flowchart: "However, if waiting for test results from Visit 10B is necessary in the judgment of the investigator, Visit 10B procedures can be performed over more than one visit but ideally should not exceed a 2-week timeframe. Trial medication is to be dispensed on the last day of Visit 10B."	Added to ensure assessments are performed for subjects with extensive gap between end of main study and starting of extension
2.2	Trial Flow Chart for Long Term Safety Trial	Added the following text to footnote "c" in flowchart and added assessments to Visit 10B: C-SSRS, ECG, directed Physical Exam, Recording of Concomitant Medications should be performed and Vital Signs, Body Weight and Laboratory samples (including urinalysis) should be collected for subjects with >3 month gap in therapy between Visit 10 and 10B. The timing of Visit 11 and all subsequent visits should be based on the trial dispensing date at Visit 10B	Added to ensure assessments are performed for subjects with extensive gap between end of main study and starting of extension

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
2.2	Trial Flow Chart for Long Term Safety Trial	Added the following to Visit 10B: Issue/Collect Subject Identification Card	This is mandatory in France
7.1	Overall Trial Design	Removed statement about ophthalmology examination completed during the Week 182 visit as this will not be done. Added reference to rater manual and deleted mention of specific scales in statement describing audio-recording procedures.	Clarification of previous clerical error and inconsistency with flow chart Clarification to ensure consistency with rater manual.
7.2	Beginning and End of the Trial	Added the following statement: Given the exploratory nature of the extension trial endpoints, the retrieved dropout approach employed in the main cohort/safety cohort trial period (initial 78 week treatment period), will not be applicable to this extension trial period. Thus, subjects who discontinue study medication during the extension trial period will be discontinued from the study.	Clarification
7.7.2.2.3	Events of Clinical Interest	Since routine MRI monitoring for safety has been discontinued, the central Reading Center is not automatically performing central reading for safety. Therefore, during the main study and the extension, the site investigator or	Clarification

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
		radiologist should perform a local reading, as necessary. In some cases, central reads for safety may be performed. In the event that an ARIA is detected, then the Sponsor may request that the MRI be submitted for central reading.	
8.2.7	Accounting for Missing Data	For the Tipping Point sensitivity analysis, stated intention to calibrate between the primary ANCOVA model and the multiple imputation model, if needed. Also, removed an errant negative sign from the exponent in the tipping point test statistic.	The tipping point sensitivity analysis is intended to report the value *c* that would need to be applied to all multiply-imputed values from the active arms, to turn a significant result, non-significant. However, it is possible that a slight difference may exist between the primary ANCOVA model and the multiple imputation (MI) model (absent any adjustment to the active arms) for the final observed dataset. Such a difference would bias the intended interpretation of *c* (i.e. some small fraction of c would represent the difference between the models, as opposed to the entirety of *c* representing the detrimental effect needed to be applied to the active arms to tip the significant result to non-significant.)

2.0 SYNOPSIS

TITLE OF TRIAL: A, Parallel-Group, Double Blind Long Term Safety Trial of MK-8931 in Subjects with Alzheimer's Disease. (Protocol No. MK-8931-017-21) (also known as SCH 900931, P07738)

ABBREVIATED TITLE: A Long Term Safety Trial of MK-8931 in AD (EPOCH)

OBJECTIVES:

Primary Trial Objectives:

1. To evaluate the safety and tolerability of MK-8931 in the long term treatment of mild to moderate Alzheimer's Disease
2. To compare the efficacy of MK-8931 on cognition and functional ability in activities of daily living in subjects with mild to moderate AD in subjects administered MK-8931 for 24 months to that of subjects administered placebo for 18 months followed by MK-8931 for 6 months.

Exploratory Trial Objective:

To compare the efficacy of MK-8931 administered to subjects for 18 months to that of subjects administered placebo for 18 months during the initial 78 week trial followed by long term treatment of MK-8931 during the long term safety trial on cognition, function, disease progression, and health economic burden at multiple time points.

Trial Design

Overview:
This is a long-term safety study (up to approximately 260 weeks) which will be available to subjects who have completed the initial 78 week trial of MK-8931 Protocol 017.

The initial 78 week trial is a double blind, placebo controlled trial to evaluate the efficacy of β-site amyloid precursor protein (APP) cleaving enzyme (BACE) inhibitor MK-8931 as a potential disease-modifying therapy in subjects with mild to moderate AD. The trial is powered to detect a clinically significant change in the two coprimary outcome measures (the Alzheimer's Disease Assessment Scale Cognitive subscale [ADAS-Cog] and the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory [ADCS-ADL] change-from-baseline scores at Week 78).

At the end of the initial 78-week trial, subjects who have completed treatment may choose to participate in this long term safety trial, during which all subjects who received placebo during the initial 78 week trial will receive active drug. The long term safety trial will start with enrollment of the first subject who completes the initial 78 week trial and chooses to participate in the long term safety trial. The long term safety trial will end when the drug either becomes commercially available or when the MK-8931 program is terminated (or less, based on local regulation). The long term safety trial is expected to have a duration of up to approximately 260 weeks (5 years) for the first subject enrolled.

Trial Governance: An independent eDMC will have the primary responsibility for monitoring safety throughout the trial.

Treatment Arms:

MK-8931 12 mg and 40 mg treatment assignments from the initial 78 week trial will be carried forward into the long term safety trial. Subjects originally on placebo will be assigned to the 40 mg dose.

The Sponsor will be unblinded following the completion of the initial 78 week trial. Sites and subjects will remain blinded during the long term safety trial. Some Sponsor personnel will remain blinded during the long-term trial, as necessary, to support the conduct of the trial and the collection of efficacy data.

Sample Size:

The enrollment target for the initial 78 week trial is 1960 subjects. It is expected that 70% of subjects will complete the initial 78 week trial, and it is estimated that 90% of those will elect to enroll in the long term safety trial, with (1960* 0.70*0.90) 1235 subjects projected to enter the long term safety trial.

Number of Trial Centers: Approximately 190-210.

Duration of Participation:

Expected maximum duration of approximately 260 weeks (5 years), with the duration of individual subject participation dependent on the timing of enrollment. Duration of participation may be limited based on local

TITLE OF TRIAL: A, Parallel-Group, Double Blind Long Term Safety Trial of MK-8931 in Subjects with Alzheimer's Disease. (Protocol No. MK-8931-017-21) (also known as SCH 900931, P07738)

regulations. Subjects who do not complete initial 78 week trial of MK-8931 protocol 017 will not be permitted to continue in the long term safety trial.

Duration of Trial:

The duration of the long term safety trial is expected to be up to approximately 5 years or until MK-8931 becomes commercially available or the MK-8931 program is terminated. Duration of the trial may be limited based on local regulations.

Key Inclusion Criteria:

Each subject must have tolerated study medication and completed the initial 78-week trial. Subjects who did not complete the initial 78 weeks with study medication but did continue in the trial and completed the scheduled visits, may be permitted to enroll in the long term safety trial.

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

Key Exclusion Criteria:

The subject is at imminent risk of self-harm, based on clinical interview or on the Columbia Suicidality Severity Rating Scale (C-SSRS), or of harm to others in the opinion of the investigator. Subjects must be excluded if they report suicidal ideation with intent, with or without a plan (eg, suicidal ideation item 4 or 5 on the C-SSRS) in the past 1 month or suicidal behavior in the past 6 months.

The subject has developed a recent or ongoing, uncontrolled, clinically significant medical condition (such as, but not limited to, diabetes, hypertension, thyroid or endocrine disease, congestive heart failure, angina, cardiac or gastrointestinal disease, dialysis, or abnormal renal function with estimated creatinine clearance < 30 mL/min) other than Alzheimer's disease such that, in the judgment of the investigator, participation in the trial would pose a significant medical risk to the subject. Controlled co-morbid conditions (including diabetes, hypertension, heart disease, etc) are not exclusionary if stable. All concomitant medications, supplements (eg Vitamin E), or other substances must be kept as stable as medically possible during the trial.

Note: urinary tract infections at screening are not exclusionary if adequately treated (as documented by repeat urinalysis).

The subject has a history of, or has developed during the initial 78 week trial evidence of long QT syndrome, QTC interval $\geq$ 470 milliseconds (for male subjects) or $\geq$ 480 milliseconds (for female subjects), or torsades de pointes. Subjects with stable bundle branch block who exceed these limits for QTc interval are eligible for the trial if judged by the investigator not to be at increased risk for Torsades

The subject anticipates receiving any of the treatments listed in Table1.

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

INVESTIGATIONAL PRODUCT, DOSE, MODE OF ADMINISTRATION

Investigational Product:

MK-8931 will be supplied as tablets of 12 mg and 40 mg . All active doses from the initial 78 week trial will be carried forward into the long term safety trial, with all subjects on active treatment continuing on their same treatment arm. Subjects originally on placebo will be assigned to 40 mg:

TITLE OF TRIAL: A, Parallel-Group, Double Blind Long Term Safety Trial of MK-8931 in Subjects with Alzheimer's Disease. (Protocol No. MK-8931-017-21) (also known as SCH 900931, P07738)

1. MK-8931 12 mg orally once daily (QD) - 12/12 treatment group:
2. MK-8931 40 mg orally once daily (QD) - 40/40 and placebo/40 treatment groups:

STATISTICAL METHODS:

Data Sets to be Analyzed:

- The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this trial.
- The All-Patients-as-Treated (APaT) population will be used for the analysis of safety data in this trial. The APaT population consists of all randomized subjects who received at least one dose of trial treatment, with subjects included in the treatment group corresponding to the trial treatment they actually received.
- It is noted that the first 200 subjects enrolled will be excluded from the primary efficacy and safety analyses, since the siDMC will have access to unblinded data from these subjects in advance of a dose decision.

Efficacy Analysis:

There are no formal hypotheses for this trial. All efficacy measurements analyzed during the initial 78 week trial will continue to be collected and analyzed in the long term safety trial. The primary endpoint is the 24-Month (6 months after the primary timepoint from the initial 78 week trial) change-from-baseline treatment difference on ADAS-Cog and ADCS-ADL.

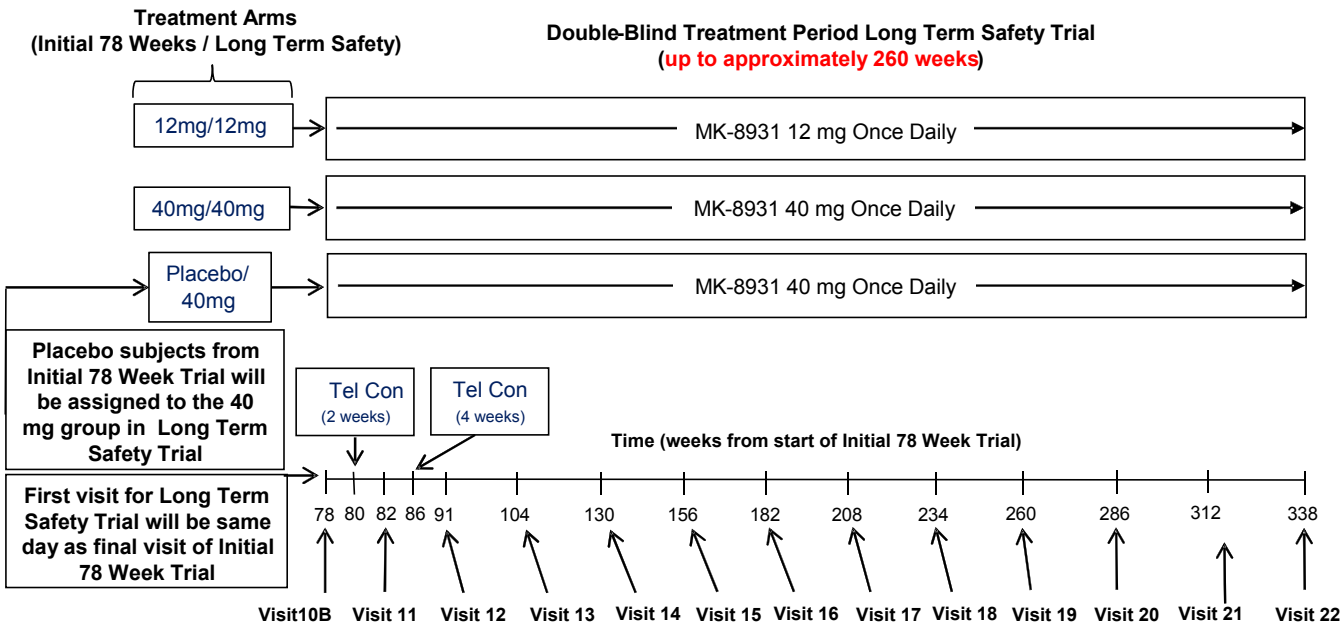
Safety Analysis: Safety and tolerability will be assessed by a clinical review of all relevant parameters including adverse events (AEs), laboratory tests, vital signs, and ECG measurements.

Safety analyses will be conducted on the cumulative data from the initial 78-week trial pooled with the data from the long term safety trial; no analyses will be conducted on the long-term safety data alone.

The broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, with a drug related AE, with an SAE, with an AE which is both drug-related and serious, or who discontinued because of an AE are considered as Tier 2 endpoints and will be analyzed. Descriptive Safety Endpoints are considered as Tier 3 events and will also be analyzed.

Interim Analyses: There are no planned interim analyses for this long-term safety trial. (The Sponsor will be unblinded following the completion of the initial 78 week trial. Some Sponsor personnel will remain blinded during the long-term trial, as necessary, to support the conduct of the trial and the collection of efficacy data.)

2.1 Trial Design Diagram for Long Term Safety Trial



2.2 Trial Flow Chart for Long Term Safety Trial

Extension Trial Period:	Treatment																	
Visit Number (continuing from Initial 78 Week Trial)	10B[b]	TC [d]	11	TC [d]	12	13	14	15	16	17	18	19	20	21	22	TC [d,f]	UV	ETV
Scheduled Week [a] (based on date of Randomization - in Initial 78 Week Trial)	78	80	82	86	91	104	130	156	182	208	234	260	286	312	338			
Extension Week (visual aid to show timing of visits in Long Term Safety Trial)	0	2	4	8	13	26	52	78	104	130	156	182	208	234	260			
Visit Window (Weeks)		+/-1	+/-1	+/-1	+/-1	+/-4	+/-4	+/-4	+/-4	+/-4	+/-4	+/-4	+/-4	+/-4	+/-4			
Informed Consent	X																	
Issue/Collect Subject Identification Card	X														X			
Record Concomitant Medication	X [c]		X		X	X	X		X		X		X		X	X	X [e]	X
Vital Signs	X [c]		X		X	X	X		X		X				X		X [e]	X
Body Weight	X [c]		X		X	X	X		X		X				X		X [e]	X
Directed Physical Exam	X [c]						X		X		X		X		X		X [e]	X
12-Lead Electrocardiogram	X [c]				X		X		X		X		X		X		X [e]	X
Skin Examination by Dermatologist																	X [e]	
Directed Skin Examination by Site Physician	X [j]						X		X		X		X		X		X [e]	
Hematology and Chemistry Samples	X [c]		X		X	X	X		X		X		X		X		X [e]	X
PK/PD Blood Samples[k]			X		X													
Urinalysis	X [c]		X		X	X	X		X		X		X		X		X [e]	X
Inclusion/Exclusion Criteria	X																	
ADAS-Cog					X	X	X		X		X		X		X			X
ADCS-ADL					X	X	X		X		X		X		X			X
CDR-SB						X	X		X		X		X		X			X
Mini-Mental State Examination (MMSE)						X	X		X		X		X		X			X

Extension Trial Period:	Treatment																	
Visit Number (continuing from Initial 78 Week Trial)	10B[b]	TC [d]	11	TC [d]	12	13	14	15	16	17	18	19	20	21	22	TC [d,f]	UV	ETV
Scheduled Week [a] (based on date of Randomization - in Initial 78 Week Trial)	78	80	82	86	91	104	130	156	182	208	234	260	286	312	338			
Extension Week (visual aid to show timing of visits in Long Term Safety Trial)	0	2	4	8	13	26	52	78	104	130	156	182	208	234	260			
Visit Window (Weeks)		+/-1	+/-1	+/-1	+/-1	+/-4	+/-4	+/-4	+/-4	+/-4	+/-4	+/-4	+/-4	+/-4	+/-4			
Neuropsychiatric Inventory (NPI)						X	X		X		X		X		X			X
Health Economic Assessment (HEA)						X	X		X		X		X		X			X
Modified Resource Utilization in Dementia (RUD) Lite						X	X		X		X		X		X			X
EuroQol Five Dimension Questionnaire (EQ-5D)						X	X		X		X		X		X			X
Columbia Suicide Severity Rating Scale (C-SSRS)	X [c]		X		X	X	X	X	X	X	X	X	X	X	X		X [e]	X
Structural Magnetic Resonance Imaging (MRI)																	X [e]	
Record Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Trial Medication	X		X		X	X	X	X	X	X	X	X	X	X			X [g]	
Assess Medication Compliance			X		X	X	X	X	X	X	X	X	X	X	X		X	X
Drug Accountability Assessment			X		X	X	X	X	X	X	X	X	X	X	X		X	X
Ophthalmology Visit (details below)	X[i]						X										X [e]	
Visual Acuity	X[i]						X										X [e]	
Posterior Eye Exams	X[i]						X										X [e]	
Fundus Photography	X[i]						X										X [e]	
Fundus Autofluorescence [h]	X[i]						X										X [e]	
SD-OCT	X[i]						X										X [e]	

a Visits scheduled during the Long Term Safety Trial will be based off of the date of randomization in the Initial 78 Week Trial for subjects enrolling into the Long Term Safety Trial immediately following the completion of the Initial 78-week Trial. Subjects with a gap in study therapy between Visit 10 and Visit 10B will begin trial assessments for Visit 10B as noted in the flowchart and continue with the visit schedule as noted in the flowchart.

b Visit 10 from the Initial 78 Week Trial and Visit 10B from the Long Term Safety Trial are considered a single visit and can be conducted on the same day. However, if waiting for test results from Visit 10B is necessary in the judgment of the investigator, Visit 10B procedures can be performed over more than one visit but ideally should not exceed a 2-week timeframe. Trial medication is to be dispensed on the last day of Visit 10B.

c C-SSRS, ECG, directed Physical Exam, Recording of Concomitant Medications should be performed and Vital Signs, Body Weight and Laboratory samples (including urinalysis) should be collected for subjects with >3 month gap in therapy between Visit 10 and 10B. The timing of Visit 11 and all subsequent visits should be based on the trial dispensing date at Visit 10B.

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

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

f Telephone contact will be performed 14 to 21 days after the final visit.

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

h Best efforts will be made to accommodate the FAF assessment. FAF images will be read by a central Reading Center designated by the Sponsor.

i Subjects who did not have a baseline ophthalmology examination completed during the initial 78 week trial or who have >6 month gap in study therapy between Visit 10 and 10B must have an ophthalmology examination completed during the Week 78 visit (10B) prior to dispensing trial medication.

j Subjects who did not have a baseline dermatology examination completed during the initial 78 week trial or who have >6 month gap in study therapy between Visit 10 and 10B must have a dermatology examination completed during the Week 78 visit (10B) prior to dispensing trial medication.

k Both plasma and dried blood spot (DBS) PK samples will be taken at each time point. The site will record the date and time of each PK sample and the date and time of the last two doses of trial medication before each PK sample. PK samples can be taken at the same time when blood samples for hematology and chemistry are taken.

3.0 TABLE OF CONTENTS

3.1 List of Tables

3.2 List of Appendices

4.0 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
Aβ	amyloid β
AChE	Acetylcholinesterase
AChEI	Acetylcholinesterase Inhibitor
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale Cognitive Subscale
ADCS-ADL	Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory
ADL	Activities of Daily Living
ADNI	Alzheimer's Disease Neuroimaging Initiative
AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
ANCOVA	Analysis of Covariance
APaT	All-Patients-as-Treated
APOE	Apolipoprotein E
APP	Amyloid Precursor Protein
AREDS	Age-Related Eye Disease Study
AST	Aspartate aminotransferase (SGOT)
BACE	β-site APP cleaving enzyme
BP	Blood Pressure
βhCG	β-Human Chorionic Gonadotropin
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CAM	Confusion Assessment Method
CBC	Complete Blood Count
CDR-SB	Clinical Dementia Rating Sum of Boxes
CDT	Counterfeit, Diversion and Tampering
CFR	Code of Federal Regulations
CI	Confidence Interval
cLDA	Constrained Longitudinal Data Analysis
CMH	Cochran-Mantel-Haenzel
CMV	Cytomegaloviruse
CRF	Case Report Form
CRO	Clinical Research Organization
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
CTD	Clinical Trial Directive
CYP	Cytochrome P450
DNA	Deoxyribonucleic Acid
DMC	Data Monitoring Committee
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECI	Events of Clinical Interest

Term	Definition
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eDMC	External (to Sponsor) Data Monitoring Committee
EDTA	Ethylenediamine Tetraacetic Acid
EIA	Enzyme immunoassay
EM	Exposure Multiples
EMA	European Medicines Agency
EQ-5D	EuroQol Five Dimension Questionnaire
EOC	Executive Oversight Committee
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FAF	Fundus Autofluorescence
FAS	Full Analysis Set
FDA	Food and Drug Administration, USA
FSH	Follicle Stimulating Hormone
FTA-ABS	Fluorescent treponemal antibody absorption
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HEA	Health Economic Assessment
HLA	Human Leukocyte Antigen
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug Application; legal instrument in the USA that allows trial of unapproved, investigational new drugs in human subjects
Investigational Product	The drug, biologic, and/or device being investigated in the current trial
IPR	Indirect Pharmacologic Response
IRB	Institutional Review Board
IU	International Units
IVRS	Interactive Voice Response System
K_i	Equilibrium Inhibition Constant
K-M	Kaplan-Meier
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LSM	Least Squares Mean
MAR	Missing at Random
MCAR	Missing Completely at Random
MFAS	Modified Full Analysis Set
MMSE	Mini-Mental State Examination
MNAR	Missing Not at Random
MRI	Magnetic Resonance Imaging

Term	Definition
mSv	millisievert
NINCDS-ADRDA	National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association
NMDA	N-Methyl-D-Aspartate
NPI	Neuropsychiatric Inventory
PD	Pharmacodynamic
PDLC	Pre-Defined Limit of Change
PET	Positron Emission Tomography
PiB	Pittsburgh compound B
P-gp	P-glycoprotein
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/Pharmacodynamic
p-tau	Phosphorylated Microtubule-Associated Protein Tau
RBC	Red Blood Cell
RNA	Ribonucleic Acid
RPE	Retinal Pigment Epithelium
RSD	Rising Single Dose
RSI	Reference Safety Information
RUD Lite	Resource Utilization in Dementia Lite Questionnaire
SAE	Serious Adverse Event
(S)AE	All adverse events, including serious adverse events
SAP	Statistical Analysis Plan
sAPPβ	N-terminal fragment secreted after β-secretase cleavage of APP
SGOT	Serum Glutamic Oxaloacetic Transaminase (AST)
SGPT	Serum Glutamic Pyruvic Transaminase (ALT)
siDMC	Standing Internal (to Sponsor) Data Monitoring Committee
SOC	System Organ Class
T-BIL	Total Bilirubin
TC	Telephone Contact
Term	Termination
THV	Total hippocampal volume
TSH	Thyroid Stimulating Hormone
Tx	Treatment
UGT1A1	Uridine diphosphate glucuronosyltransferase 1A1
ULN	Upper Limit of Normal
Unsched	Unscheduled
USA	United States of America
WBC	White Blood Cell

5.0 INTRODUCTION

5.1 Therapeutic Rationale

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

Alzheimer's disease is characterized by specific histopathological features including amyloid deposits (plaques), neurofibrillary tangles, and neuronal degeneration. The "amyloid hypothesis" posits that amyloid-β (Aβ) peptides aggregate into complexes, such as fibrils and plaques, which subsequently trigger the development of tau-related neurofibrillary tangles. These tangles are thought to be the more proximal cause of neuronal degeneration. Aβ pathology appears to begin years before the onset of AD and is thought at some point to trigger tau pathology, neural degeneration, and the subsequent gradual emergence of clinical symptoms. As amyloid plaques continue to accumulate, tangle pathology spreads to a variety of brain regions, leading to progressive neuronal degeneration, brain atrophy, and cognitive decline.

Aβ peptides are produced when amyloid precursor protein (APP) is cleaved by three distinct proteases: α-secretase, BACE1 (β site APP cleaving enzyme 1; also known as β-secretase), and γ-secretase. Most APP is processed by α and γ-secretases to generate nonamyloidogenic peptides. However, 5-10% of APP is cleaved by BACE1 and γ-secretase to generate pathogenic Aβ peptides (Aβ40 and Aβ42). Deletion of BACE1 in mice eliminates Aβ in both the plasma and the brain. Thus, inhibition of BACE1 is a potential therapeutic strategy for slowing or halting progression of AD.

MK-8931 is a potent BACE1 inhibitor being developed for the treatment of AD. It has been shown to reduce Aβ levels in the cerebrospinal fluid (CSF) and brain of rodents and primates. MK-8931 also reduces Aβ in human CSF. In Phase 1 trials, MK-8931 has been generally safe and well tolerated (see Investigator's Brochure). These results suggest that MK-8931 may reduce Aβ production in humans and could potentially slow progression in subjects with mild to moderate AD. Detailed information about MK-8931 including preclinical studies, pharmacokinetics and other relevant information is provided in the Investigator's Brochure.

5.2 Subject Population Rationale

This long term safety trial will start with enrollment of the first subject who completes the initial 78 week trial and will end when the drug either becomes commercially available or when the MK-8931 program is terminated.

Subjects may start or switch to another cholinesterase inhibitor or memantine during this trial. Other additional treatments must not be initiated during the trial except as otherwise specified in this protocol.

Details about specific benefits and risks for subjects participating in this clinical trial can be found in the accompanying Investigator's Brochure and Informed Consent documents.

5.3 Trial Design Rationale

This is a parallel group, multi-site, double-blind, long term safety trial to provide access to MK-8931 before it is commercially available, to estimate the effects of delayed start of MK-8931, and to evaluate the safety and tolerability of two doses of MK-8931 in the extended treatment of mild to moderate AD. MK-8931 is hypothesized to exert disease modifying effects in subjects with AD. A delayed-start design may provide supportive evidence of disease modification in AD if the treatment effect is sustained and greater in the group of subjects that starts the active treatment earlier as compared to the group of subjects with a substantial delay in the start of active treatment. Results from the long term safety trial will also provide data regarding the sample sizes necessary for, and the feasibility of, delayed start studies with disease modifying therapeutics for AD. In addition, this long term safety trial will be used to further assess the long term effects of MK-8931 on disease progression, health economic effects, and the safety and tolerability of MK-8931. Some Sponsor personnel will be unblinded following the completion of the initial 78-week trial. Some Sponsor personnel will remain blinded during the long-term trial, as necessary, for the conduct and collection of efficacy data, including the 24-month timepoint to support the primary objective regarding efficacy. Details are included in the Sponsor's blinding document.

Once a subject enters the long term safety trial, participation will continue until one of the following occurs: 1) MK-8931's development is terminated for mild to moderate AD (eg. due to a lack of efficacy), 2) MK-8931 is approved by regulatory agencies and becomes commercially available, 3) the subject voluntarily withdraws or 4) the subject is discontinued for safety reasons. The long term safety trial is expected to continue up to five years after the first subject enters the trial.

5.4 Outcome Measures Rationale

The primary clinical measures in this trial are the Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-Cog) and the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL). The ADAS-Cog is a measure of cognition while the ADCS-ADL is a measure of functional ability in activities of daily living. The measures are validated instruments that are acceptable to regulatory agencies, have been used previously in drug trials in this patient population, and can reliably detect clinically relevant changes in AD.

After the initiation of P017, the FDA issued guidance to Sponsors indicating that all trials with BACE1 inhibitors that are longer than two weeks in duration must include routine monitoring of skin. There have been observations in the literature that mice lacking the gene for BACE2 have reduced pigment [30]. In recently completed studies of MK-8931 in two pigmented species (mouse and rabbit), reduced hair pigment was observed within four weeks of treatment in all animals, which was reversible with cessation of treatment. On microscopic examination, normal skin histology was observed except for loss of pigmentation in the hair follicle/shaft. There was no loss of melanocytes. All phases of the hair cycle were present, and no inflammatory or degenerative changes in hair follicles, sebaceous glands, epidermis, or dermis were observed. In contrast to these observations in mouse and rabbit, no change in hair pigment or skin and retinal histology have been observed in monkeys treated for up to 9 months with MK-8931 at exposures 36-fold above those achieved at the highest dose of MK-8931 tested in P017 (60 mg). Furthermore, no adverse events of skin hypo- or depigmentation have been reported thus far in prior human trials of MK-8931.

A review of preclinical data and the FDA request with a panel of expert dermatologists indicated the overall risk to patients is minimal. The risk of vitiligo, with loss of dermal melanocytes, was seen as low. If vitiligo were observed, medical management was recommended without discontinuation of study medication, given that vitiligo is not associated with significant morbidity or mortality. Hypopigmentation was viewed as being a more likely finding with BACE inhibitor treatment, rather than vitiligo. Hypopigmentation by itself was also not seen as requiring discontinuation of study medication. Therefore, baseline and post-treatment dermatology assessments were added to this protocol to document the incidence of hypopigmentation, not to detect a significant safety risk. Patients will be informed of the risk of hypopigmentation and instructed to use sun screen in affected areas if exposed to sunlight. A long-term risk may be increased skin cancer due to sun damage to the skin. Incident cases of hypopigmentation should be referred to a specialist for appropriate diagnosis and treatment, if clinically indicated. If no difference is seen in the occurrence of hypopigmentation between the placebo and MK-8931 groups after 300 subjects/group are evaluated at six months in the MK-8931 program (P017 and P019), the eDMC may recommend the discontinuation of the routine skin examinations in a future amendment. Sites would continue to collect skin-related adverse events and refer subjects for further dermatologic evaluation as needed.

5.5 Dose and Administration Rationale

Subjects who tolerated study medication and completed the initial 78-week trial of Protocol 017 may enroll in this long term safety trial. Those subjects who did not complete treatment in the initial 78-week trial, but did continue in the trial and completed the scheduled visits, may be permitted to enroll in this long term safety trial. Subjects who received the 12 mg or 40 mg dose during the initial 78-week trial will continue to receive the same dose in this long term safety trial. They will be referred to as the 12/12 and the 40/40 groups respectively. Subjects who received placebo during the initial 78 week trial will receive the 40 mg dose during this long term safety trial. They will be referred to as the placebo/40 group.

The 40 mg dose has been shown to substantially inhibit CSF Aβ. The 12 mg dose produces a more moderate reduction in CSF Aβ and is included since the long term safety of greater inhibition is unknown. Using PK/PD modeling and simulation, 12 mg and 40 mg doses are projected to reduce CSF Aβ by at least 50% and 75%, respectively, in more than 90% of subjects. It is unknown how much Aβ lowering is optimal from the perspective of both safety/tolerability as well as efficacy. Subjects who received placebo during the initial 78 week trial will be treated with the 40 mg dose in the long term safety trial to provide additional information about the long term safety of MK-8931 and to estimate the clinical effects of delayed start of this higher dose.

6.0 TRIAL OBJECTIVES

6.1 Primary Trial Objectives

There are two primary objectives in which the subjects who received 40 mg / 40 mg will be compared to those who received placebo / 40 mg. Similarly, subjects who received 12 mg / 12 mg will be compared to those who received placebo / 40 mg. The two objectives are as follows:

1. To evaluate the safety and tolerability of MK-8931 in the long term treatment of mild to moderate Alzheimer's Disease.

2. To compare the efficacy of MK-8931 administered to subjects for 24 months to that of subjects administered placebo for 18 months followed by MK-8931 for 6 months using endpoints at follows.

    - the change-from-Baseline score in the ADAS-Cog at Week 104 (Visit 13).

    - the change-from-Baseline score in the ADCS-ADL at Week 104 (Visit 13).

6.2 Exploratory Trial Objective

To compare the efficacy of MK-8931 administered to subjects for 18 months to that of subjects administered placebo for 18 months during the initial 78 week trial followed by long term treatment of MK-8931 in the long term safety trial on cognition, function, disease progression, and health economic burden at multiple time points.

7.0 INVESTIGATIONAL AND ANALYSIS PLAN

7.1 Overall Trial Design

Overview

This is a parallel group, multi-site, double-blind, long term safety trial of MK-8931 in subjects with mild to moderate AD.

Trial Governance Committees

An independent external Data Monitoring Committee (eDMC) will have the primary responsibility for monitoring safety throughout the trial. In addition an internal Executive Oversight Committee (**EOC**) of the sponsor will receive recommendations throughout the trial from the eDMC and is responsible for acting upon the recommendations of the eDMC. The composition, activities, and responsibilities of these trial governance committees will be described in the eDMC charter.

The eDMC will review data in a manner such that the trial team, investigators, subjects, and vendors will not have access to the unblinded data.

The EOC will not have access to unblinded data or reports unless it is deemed necessary by the eDMC in order to act upon an eDMC recommendation. The EOC will be completely independent of, and separate from, the trial team performing the medical monitoring and supervising the operational aspects of the protocol.

Summary

Subjects who have completed the initial 78 week trial and tolerated study medication may be eligible for enrollment into this long term safety trial, during which all subjects who received placebo during the initial 78 week trial will receive active drug. Subjects who did not complete the initial 78 week trial will not be permitted to continue into the long term safety trial.

The two primary efficacy endpoints are the ADAS-Cog and ADCS-ADL scores. Additional Endpoints include the CDR-SB, the NPI and MMSE scores; and health economic and quality of life outcomes including a modified Resource Utilization in Dementia [RUD] Lite Questionnaire, the Health Economic Assessment [HEA]) and the EuroQol Five Dimension Questionnaire (EQ-5D).

Safety and tolerability will be assessed by a clinical review of all relevant parameters including AEs, laboratory tests, vital signs, and ECG measurements. The same safety parameters and AEs designated as being of special interest during the initial 78 week trial will continue to be monitored in the long term safety trial, as follows:1) delirium; and 2) rash ECI (see **Section 7.7.2.2.3**). Some of these AEs are combined into composite endpoints for formal safety analyses (see Section 7.7.2.2.3.).

Regarding MRI monitoring, the US FDA had noted the occurrence of imaging abnormalities believed to represent cerebral vasogenic edema in association with the investigational use of compounds that are intended to treat AD by reducing β-amyloid in the brain. These imaging abnormalities, described by Salloway et al.[1], have, in the majority of instances, been asymptomatic and their presence has been detected by routine MRI scans. Symptoms, when present in association with such imaging abnormalities, have been reported to include headache, worsening cognitive function, alteration of consciousness, seizures, unsteadiness, and vomiting. In most instances, the occurrence of such imaging abnormalities, even when symptomatic, has not required treatment beyond discontinuation of the investigational compound, with imaging abnormalities then resolving; infrequently, high-dose steroid therapy has been administered in the presence of prominent symptoms.

Previous regulatory guidance required that all subjects have an MRI scan during Screening in order to qualify for the trial and, subsequently, routine MRI scans for safety monitoring. Following a comprehensive review of the existing data, the FDA has recently updated this guidance stating that serial clinical and MRI monitoring will no longer be required as a matter of course in clinical trials of small molecule drugs that may affect β-amyloid. Therefore, routine MRI safety monitoring is not included in this long term safety trial. MRI scans are collected during the initial 78 week trial to assess eligibility and for brain structure volumetric outcome measures. MRIs may be performed at a post-treatment visit for safety monitoring if clinically indicated as determined by the investigator (e.g., in follow-up to an AE). If amyloid-related imaging abnormalities are identified during the trial they should be handled as follows.

1) Trial medication should be discontinued if an imaging abnormality consistent with macrohemorrhage appears or a **clinically symptomatic** incident vasogenic edema, microhemorrhage, or superficial siderosis is seen.
2) If symptomatic cerebral vasogenic edema occurs, MRI scans should be repeated within three to four weeks to assess stability and then performed every four to six weeks (or as clinically indicated) until the vasogenic edema resolves. Treatment with high dose dexamethasone can be considered, as suggested by the US FDA, if associated symptoms are severe.
3) For subjects who present with new clinically symptomatic microhemorrhages or superficial siderosis, an MRI re-scan at three to four weeks should be performed in order to evaluate their stability.

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

5) For macrohemorrhage (symptomatic or asymptomatic), subjects must be discontinued from trial medication and cannot resume dosing.

[redacted]

Ophthalmologic evaluation of subjects with AD can be challenging. Experts have noted that assessment of visual acuity can be confounded by cognitive deficits[20] which could limit its usefulness for assessing drug effects. On the other hand, SD-OCT is a sensitive method for evaluating retinal structure with micrometer resolution. [redacted] Additional ophthalmologic assessments included visual acuity test, SD-OCT measurements of other retinal layers, posterior eye exam including dilated funduscopy, and fundus photography. Fundus autofluorescence (FAF) was also included at centers with the appropriate capabilities. During the initial 78-week trial ophthalmologic assessments were initially conducted at ophthalmology centers at Screening, Week 13, 26, 52 and 78, and Early Termination Visit.

Based on the recommendation of the eDMC in March 2015, after reviewing results from the initial 78-week trial and available data from an ongoing trial in prodromal AD patients (MK-8931-019) the frequency of ophthalmologic monitoring was modified. Within the long term safety trial, subjects who did not have a baseline ophthalmology examination during the initial 78 week trial or who have >6 month gap in study therapy between Visit 10 and 10B will have an ophthalmology examination completed at the Week 78 visit (visit 10B). In addition, subjects participating in the long term safety trial will have an ophthalmology examination completed at Week 130.

Preclinical studies initially noted slight reduction of iris pigment in rabbits, as described in the IB. More recent studies failed to replicate the effect on iris pigment (see IB). Iris pigment monitoring is not included in this trial.

There is no randomization for this long-term safety trial, aside from that employed for the initial 78 week trial.

Subjects will be asked to provide blood samples for pharmacokinetic (PK) analyses to determine plasma concentrations of MK-8931. This information will be used to develop a population PK model and to explore the exposure-response relationship in the trial population. Pharmacokinetic blood samples will be collected at the following visits:

- Week 4 of extension (week 82 overall)
- Week 13 of extension (week 91 overall)

Under Amendment 21, both plasma and dried blood spot (DBS) PK samples will be collected at each timepoint as noted in the Trial Flow Charts. Details regarding use of samples for PK and PK/PD modeling will be specified in the modeling analysis plan document.

For subjects who sign a separate consent form for pharmacogenetic analysis, blood samples for pharmacogenetic analysis will also be collected.

Quality control is an essential part of all clinical trials. In an effort to maintain quality control of the clinical ratings, this trial will include a review of the ratings by outside expert(s). This review may include all available medically relevant data, a narrative summary of the subject's history, and a review of video/audio recordings of key clinical interviews performed.

All sites must ensure raters are properly qualified and trained prior to the administration of any clinical assessments. Rater performance on these assessments will be carefully evaluated and monitored to ensure and maintain adequate reliability. Details will be specified in the **Manual of Assessments**. Raters must be approved by the sponsor, which will typically require successful completion of a trial specific rater training program. To ensure the continued quality of the assessments, raters will be asked to audio record interviews and ratings through Week 104, as directed in the manual from the rater training vendor. Some or all of these recorded interviews will be reviewed by outside experts. Raters will be provided feedback on the quality of their interviews and ratings by the outside experts by e-mail, telephone or in meetings in order to develop and maintain good rater reliability. Based on this feedback, raters may change their initially recorded scores if errors are identified. Raters who do not perform adequately may be required to undergo additional remediation or may be replaced.

While concerns have been raised that video/audio recordings could theoretically compromise subjects' privacy, this issue must be balanced with the needs to conduct methodologically adequate and scientifically rigorous trials that are capable of testing the key hypotheses. Given that the key endpoints in this trial involve subjective judgments, monitoring the adequacy of subject interviews and ratings is essential and part of good research methodology. Prior studies have clearly

demonstrated that the failure to adequately monitor such ratings can substantially increase the risks of failed trials[7,8]. Recorded interviews will be encrypted using state of the art methods to ensure privacy. Recordings will only be reviewed by approved trial personnel for quality control purposes and will be destroyed within two years of the completion of the trial unless local regulatory authorities or Institutional Review Boards or Independent Ethics Committees (IRBs/IECs) have different requirements for storage.

Subjects may participate in this protocol and continue to participate in certain observational studies, if approved by the Sponsor. These studies must involve only limited cognitive testing (eg, annual) and subjects will not be permitted to undergo any non-protocol cognitive testing within the two months prior to Week 104.

7.2 Beginning and End of the Trial

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

This long term safety trial will start with enrollment of the first subject who completes the initial 78 week trial and will end when the drug either becomes commercially available or when the MK-8931 program is terminated. This long term safety trial has an expected maximum duration of approximately 260 weeks, with the duration of individual subject participation dependent on the timing of enrollment. Duration of participation may also be limited based on local regulations.

Each subject is considered to have ended participation in the trial when he/she has completed the last protocol-specified contact (eg, visits or telephone contacts) or has prematurely discontinued from the trial. A subject will be considered a completer of this long term safety trial if he/she is still continuing in the trial when the trial is stopped.

A subject is considered to have discontinued after he/she has withdrawn consent or has been discontinued under the conditions specified in **Section 7.3.3**. All applicable activities scheduled for the final trial visit should be performed at the time of treatment discontinuation as defined in the long term safety trial Flow Chart in **Section 2.2**.

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

Each subject will be monitored for the occurrence of AEs beginning immediately after the subject has signed informed consent through 14 days after cessation of treatment. Follow-up procedures related to pregnancy or existing SAEs may continue beyond the end of the clinical trial.

Given the exploratory nature of the extension trial endpoints, the retrieved dropout approach employed in the main cohort/safety cohort trial period (initial 78 week treatment period), will not be applicable to this extension trial period. Thus, subjects who discontinue study medication during the extension trial period will be discontinued from the study.

7.3 Trial Population

The trial population is adult subjects with a diagnosis of AD who completed the initial 78 week trial.

7.3.1 Subject Inclusion Criteria

A subject must meet all the criteria listed below to participate in the trial. Subjects must

1. have tolerated study medication and completed the initial 78 week trial. Subjects who did not complete the initial 78 weeks with study medication but did continue in the trial and completed the scheduled visits, may be permitted to enroll in the long term safety trial
2. have a trial partner who is reliable and competent. The trial partner must have a close relationship with the subject, have face to face contact at least 3 days/wk for a minimum of 6 waking hours/wk (or more, based on local requirements), be willing to accompany the subject to all trial visits, and be willing to monitor compliance of the administration of the trial medication. The trial partner should understand the nature of the trial and adhere to trial requirements (eg, dose, visit schedules, and evaluations). It is recommended that the trial partner accompany the subject to all trial visits.
3. sign (or legal representative sign) the informed consent form in accordance with local requirements, after the scope and nature of the investigation have been explained.

7.3.2 Subject Exclusion Criteria

A subject meeting any of the exclusion criteria listed below must be excluded from participating in the trial. Subject

1. is at imminent risk of self-harm, based on clinical interview or on the Columbia Suicidality Severity Rating Scale (C-SSRS), or of harm to others in the opinion of the investigator. Subjects must be excluded if they report suicidal ideation with intent, with or without a plan (eg, suicidal ideation item 4 or 5 on the C-SSRS) in the past 1 month or suicidal behavior in the past 6 months.
2. has developed a recent or ongoing, uncontrolled, clinically significant medical condition (such as, but not limited to, diabetes, hypertension, thyroid or endocrine disease, congestive heart failure, angina, cardiac or gastrointestinal disease,

dialysis, or abnormal renal function with estimated creatinine clearance < 30 mL/min) other than Alzheimer's disease such that, in the judgment of the investigator, participation in the trial would pose a significant medical risk to the subject. Controlled co-morbid conditions (including diabetes, hypertension, heart disease, etc) are not exclusionary if stable. All concomitant medications, supplements, or other substances must be kept as stable as medically possible during the trial.

Note: urinary tract infections at Visit 10B are not exclusionary if adequately treated (as documented by repeat urinalysis).

3. has a history of, or has developed during the initial 78 week trial evidence of long QT syndrome, QTC interval ≥ 470 milliseconds (for male subjects) or ≥ 480 milliseconds (for female subjects), or torsades de pointes.
4. anticipates receiving any of the treatments listed in **Table 1** during the study.

Table 1 Prohibited Medications, Supplements, and Other Substances

Anti-amyloid agents (eg, tarenflurbil, tramiprosate)
Anti-amyloid antibodies (eg, bapineuzumab)
Anti-amyloid vaccine (Subjects who received placebo in a vaccine trial may participate in this trial.)
CYP3A4 inducers (strong) including: rifampicin and St. John's Wort, phenytoin, carbamazepine **Exceptions:** Use of the following is acceptable: topical use; short-term (<2 weeks) oral treatment during the trial; use of oral St. John's Wort <300 mg three times a day during the trial, regardless of duration.
Drugs known to cause ocular changes or damage (eg, chloroquine, hydroxychloroquine [sometimes used for arthritis], many anti-malarial treatments, ethambutol for tuberculosis, amiodarone for ventricular arrhythmias, and tamoxifen for breast cancer)

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

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

7.3.3 Subject Discontinuation Criteria

A subject may discontinue from the clinical trial at any time for any reason. A subject **must** be discontinued from the trial if the subject or legal representative (such as a parent or legal guardian) withdraws consent.

The investigator should stop trial medication in any case in which emerging effects are of unacceptable risk to the individual subject, or if unmanageable factors arise

that may interfere significantly with the trial procedures and/or the interpretation of results.

A subject must discontinue trial medication for any of the following reasons:

1. The subject or legal representative withdraws consent;
2. Elevated ALT, AST, or T-BIL meeting any one of the following criteria:
    A. ALT or AST ≥ 8 x ULN;
    B. ALT or AST ≥ 5 x ULN for more than 2 weeks;
    C. ALT or AST ≥ 3 x ULN and T-BIL ≥ 2 x ULN at the same visit;
    D. ALT or AST ≥ 3 x ULN with the appearance of symptoms indicating hepatitis (eg, worsening fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia).

    Exception: if elevations are determined to be due to some other medical condition, subject may resume trial medication with Sponsor approval;
3. An imaging abnormality consistent with macrohemorrhage appears (see details in **Section 7.1**);
4. QTc prolongation (defined as QTc interval > 500 ms or QTc change from baseline > 60 ms, based on the average of three measurements using the Fridericia formula for correction).

    Exception: if QTc change from baseline > 60 ms is determined to be due to some other medical condition, or if subject has a new onset of bundle branch block, subject may continue treatment with Sponsor approval;
5. The subject develops a form of dementia that is not Alzheimer's disease, including but not limited to, dementia due to HIV infection, head trauma, vascular disease, Parkinson's disease, frontotemporal dementia, or Huntington's disease, as determined by the investigator;
6. The subject develops a severe rash. For the purpose of this program, a "**severe rash**" is defined as one of the following:
    - A vesicular rash (ie, one with blistering lesions) that is not clearly caused by herpes simplex virus or contact allergy such as poison ivy AND has EITHER a) extensive body surface area (BSA) involvement OR b) involves oral/mucosal surfaces
    - Stevens-Johnson Syndrome, erythroderma, or toxic epidermal necrolysis
    - DRESS syndrome
7. The subject develops an uncontrolled clinically significant rash defined as follows:
    - A clinically significant rash (see **Section 7.7.2.2.3**) that is not controlled by topical medications or oral medications such as antihistamines (detailed in the Rash Guidance Document), and

- A clinically significant rash that causes intolerable discomfort for the subject.

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

Subjects who are unwilling to continue should proceed to a termination visit. At a minimum, the following information should be collected when a subject discontinues:

1. The reason the subject discontinued;
2. The date of the last dose of test products from the trial;
3. The date of the last assessment and/or contact. A follow-up contact (telephone or visit) will be arranged as appropriate;
4. (Serious) Adverse events;
5. Compliance with the test product administration as specified in this protocol;
6. Final Assessments:
7. Every effort should be made to ensure that all procedures and evaluations scheduled for the final trial visit are performed (**Section 2.2**, Trial Flow Chart)
8. Retrieve all investigative products and test articles from the subject.

7.3.4 Replacement of Subjects

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

7.4 Treatments

7.4.1 Trial Treatments

7.4.1.1 Treatments Administered

The rationale for selection of doses to be used in this trial is provided in **Section 5.5** – Dose and Administration Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

Subjects who received the 12 mg or 40 mg dose during the initial 78-week trial will continue to receive the same dose in this long term safety trial. They will be referred to as the 12/12 and the 40/40 groups respectively. Subjects who received placebo during the initial 78 week trial will receive the 40 mg dose during this long term safety trial. They will be referred to as the placebo/40 group.

7.4.1.2 Method of Treatment Assignment, Randomization, and/or Stratification

During the initial 78-week trial, randomization was implemented through the use of a central interactive voice response system (IVRS). The treatment arm to which

subjects were randomized during the initial 78 week trial will determine the treatment received during the long term safety trial – as described in Section 7.4.1.1.

Though not planned, it is possible that an active dose arm (eg, 40 mg) could be dropped depending on eDMC review. In the event that only one active dose remains while enrollment is still ongoing, then subjects in the dropped dose arm will be re-assigned to receive the remaining active dose.

7.4.1.3 Selection and Timing of Dose for Each Subject

7.4.1.3.1 Selecting the Dose for Each Subject

The rationale for the selection of doses to be used in this trial is presented in **Section 5.5**.

7.4.1.3.2 Determining the Timing of Dose Administration for Each Subject

The trial medication should be administered by the subject, by the subject's trial partner, or by a caregiver. Each subject should take one tablet at the same time every day. For each of the treatment groups, one tablet equals one dose of trial medication as summarized below:

- 12/12 group: MK-8931 12 mg (One Tablet)
- 40/40 and placebo/40 groups: MK-8931 40 mg (One Tablet)

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

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

7.4.1.4 Blinding Trial Treatments

All doses of MK-8931 will be identical in appearance and will be packaged identically so that the treatment blind is maintained for the subject and investigator. The sponsor will be unblinded at the completion of the initial 78-week trial.

See **Section 7.7.2.5.3** for a description of the method of unblinding a subject during the trial, should such action be warranted.

7.4.1.5 Investigational Medicinal Products

The investigator has the responsibility for taking all steps to maintain appropriate records and to ensure appropriate supply, handling, storage, distribution, and usage

of these materials in accordance with the protocol and any applicable laws and regulations.

7.4.1.5.1 Identity of Investigational Medicinal Products

The trial medication will be provided as a tablet formulation to support all subjects in the trial. Please see the Investigator's Brochure for a full description of the investigational medicinal product.

7.4.1.5.2 Source

The sponsor will provide trial medication as follows: MK-8931 12 mg tablets; MK-8931 40 mg tablets.

7.4.1.5.3 Labeling

MK-8931 bottle labels should include the following information and comply with the regulatory requirements appropriate for clinical site: Dosing directions will state, “Take 1 tablet once a day”.

7.4.1.5.4 Packaging

Trial medication will be provided in bottles.

At the visits specified in the Trial Flow Chart (**Section 2.2**), the site will dispense medication using the IVRS system. The site will provide the medication to the caregiver/trial partner and may provide a ‘calendar sleeve’ to attach to the subject’s trial medication bottle. Additional instructions regarding the calendar sleeves will be provided to sites.

7.4.1.5.4.1 Calendar Sleeves for Study Medication Bottles

In addition to routine surveillance of subject trial medication compliance, subjects/ caregiver/trial partner may be given trial medication ‘calendar sleeves’ which affix to the exterior of trial medication bottles to help subjects remember when to take trial medication. The intention of the sleeves is to assist the subject/caregiver/trial partner to remember when the subject missed a dose. The sponsor will provide the sleeve to the sites and sites personnel will slide them onto each bottle. The site will then instruct the caregiver/trial partner on how to make sleeve subject specific (ie document on the ‘calendar sleeve’ the date to start taking trial medication, bottle number).

When the subject/caregiver/trial partner returns to the clinical site, the site will perform a pill count and also review the ‘calendar sleeves’(if they have utilized the sleeve), to verify pill count and any possible missed or extra doses taken. If there is a discrepancy between the bottle and the ‘calendar sleeve’ then the physical pill count will be the final decision to be documented in the eCRF. Discrepancies should

be documented in the site's source documents and the reasoning for what was ultimately recorded in the eCRF.

7.4.1.5.5 Storage

Trial treatment supplies must be stored in a secure, limited-access location under the storage conditions specified on the supply label. Site storage conditions should be monitored by the site personnel for adherence to label specifications and reviewed during site visits.

7.4.1.5.6 Dispensing

The investigator or qualified designee(s) will dispense trial treatments at the designated site(s) to subjects who have provided written informed consent and have met the entry criteria. Clinical supplies may not be used for any purpose other than that which is stated in this protocol.

See the Trial Flow Chart in **Section 2.2** for a schedule of when clinical supplies are to be dispensed to the subjects.

7.4.1.5.7 Replacement of Investigational Product

Replacement of trial medication will be performed only in limited cases (eg, lost, broken, or spilled treatment bottles). In the event that replacement units are needed, the IVRS help desk should be contacted. The IVRS help desk will be responsible for obtaining permission to release replacement units from the sponsor.

7.4.1.5.8 Investigational Medicinal Product Accountability

Accurate and current accounting of the dispensing and return of investigational products will be maintained on an ongoing basis by a member of the trial site staff:

- Investigational medicinal products dispensed to each subject will be recorded in the trial-specific Subject IMP Accountability Log (or equivalent document approved by the sponsor).

The Subject IMP Accountability Log will be verified by the sponsor's trial monitor. The original Subject IMP Accountability Log will be approved by the investigator and retained at the trial site and a copy supplied to the sponsor when the trial is complete.

Each subject will be instructed by the investigator or designee to return all unused and partially used test articles to the site at all protocol-specified visits.

The sponsor's trial monitor will instruct the site on the return of all investigational products supplies. Inventory records must be readily available for inspection by the trial monitor and/or auditor, and open to government inspection at any time.

7.4.2 Non-Trial Treatments

Subjects who are provided non-trial treatments, such as day care, may continue these through the trial. The frequency should not change unless medically indicated. Day care attendance on the day before clinic visits and cognitive testing should remain stable through the protocol. For example, a subject who attends day care the day prior to baseline testing should also attend day care on the day before all subsequent visits that include ADAS-Cog and ADCS-ADL testing.

7.4.2.1 Prior and Concomitant Medications

7.4.2.1.1 Medications, Supplements, and Other Substances Prohibited During the Trial

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

During the trial, initiation of treatment with medications known to be associated[21,22] with substantial increased risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis should be avoided when possible. Subjects who have been safely treated with at least one routine course of treatment with these medications in the past are exempted from this requirement. Examples of such medications are included below. The sponsor should be consulted for questions about specific medications.

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

7.4.2.1.2 Concomitant Medications, Supplements, and Other Substances Allowed During the Trial

Medications, supplements, and other substances allowed during the trial include, but are not limited to, those listed in Table 2. Note that the use of any concomitant medication must relate to the documented medical history, prophylaxis, or an adverse event of the subject.

Table 2 Medications, Supplements, and Other Substances Allowed During the Trial

Acetylcholinesterase inhibitors (eg, donepezil, tacrine, rivastigmine, galantamine)
Memantine
Huperzine A
Vitamin E
Herbal supplements from *Ginkgo biloba*, ginseng, *Huperzia serrata* (Qian Ceng Ta)
Medical foods/supplement (eg, Axona®, Souvenaid®)
Estrogens and estrogen-like compounds
Antihypertensives
Nonsteroidal anti-inflammatory drugs (NSAIDs)
Cycloxygenase 2 inhibitors
Neuroleptics: asenapine, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone
Analgesics/Narcotics: Use of ≤ 2 doses/week or short-term use (<1 month) of more than 2 doses/week for temporary conditions is acceptable (eg, codeine, morphine , hydromorphone, oxycodone, propoxyphene (Darvon) and its variations, & combination products that contain a narcotic).
Sedative/benzodiazepines: Use of the following medications is acceptable: trazodone, mirtazapine, zaleplon ≤ 5 mg, zopiclone ≤ 7.5 mg, eszopiclone ≤ 3 mg, zolpidem ≤ 5 mg, or lorazepam ≤ 1.0 mg. For other medications in this category not specified here, please contact the Sponsor for guidance.
Antidepressants: bupropion, citalopram (40 mg or less), escitalopram, fluoxetine, mirtazapine, paroxetine, sertraline, venlafaxine. Use of 50mg or less at night of nortriptyline or desipramine during the trial is acceptable.
Pramipexole, ropinirole, and L-dopa (for sleep only): Treatment for restless leg syndrome
Pregabalin and gabapentin: Treatment for neuropathic pain
Anticholinergic medications: Daily use of anticholinergic medications for incontinence (eg, oxybutynin, tolterodine, darifenacin, solifenacin, trospium, fesoterodine), nasal spray for rhinorrhea (ipratropium) or inhalants for pulmonary disorders (eg, tiotropium) is acceptable.
Rifampicin and St. John's Wort: Topical use, short-term (<2 weeks) oral treatment during the trial, use of oral St. John's Wort <300 mg three times a day during the trial, regardless of duration
Corticosteroids: Low dose oral treatment with the equivalent of 10 mg prednisone or less, short-term (<3 weeks) oral treatment with the equivalent of 60 mg prednisone or less, if needed for management of rash, local injections into joints or bursae, topical use, inhaled or nasal use
Selective H1 blockers, selective H2 blockers, and topical anti-pruritic treatments for treatment of rash during the trial, as specified in the Rash Guidance Document

7.4.3 Procedures for Monitoring Subject Compliance With Administration of Trial Treatments

At all protocol-specified visits, the investigator or qualified designee is to record whether treatment had been taken per protocol in the preceding interval.

7.5 Trial Schedule

The visit-by-visit schedule of trial activities is provided in the Trial Flow Chart in **Section 2.2**.

The timing of each subject visit is relative to Study Day 1 of that subject, with Study Day 1 defined as the date of randomization into the initial 78-week trial (which should also be the date of the first administration of trial medication in the initial 78 week trial) (**Section 7.4.1.1**).

All visits should be performed within the windows specified in **Section 2.2**, the Long Term Safety Trial Flow Chart. Every attempt should be made to have each subject attend each visit as scheduled. However, if a subject is unable to attend a visit within the specified windows, the visit should be scheduled as closely as possible to these windows. A subject should not miss a protocol-specified visit due to scheduling difficulties.

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

7.6 Trial Procedures

The Trial Flow Chart in **Section 2.2** summarizes the trial procedures to be performed at each visit. Individual trial procedures are described below.

The order in which evaluations are completed is at the discretion of the investigator in order to best accommodate the needs of the subject/caregiver as well as the logistical considerations of the coordinator/staff.

In order to minimize variability of evaluations, it is preferred that the same individuals perform the same types of evaluations for all subjects at each trial site. In addition, blood samples for a visit should NOT be collected prior to the testing of the clinical outcomes.

1. Explain Trial and Obtain Written Informed Consent

   The investigator or qualified designee will explain the trial to the subject, answer all of his/her questions, and obtain written informed consent before performing any trial-related procedure. A copy of the informed consent will be given to the subject (see **Section 9.1.2** for further description of the Informed Consent).

   Given the trial population and the duration of the trial, it is possible that a subject's cognition may decline to a point where they no longer have capacity to provide informed consent. If this occurs, the site should obtain consent to continue in the trial from the subject's legally acceptable representative and in accordance with local standards and requirements. The subject's assent to continue should also be obtained.
2. Issue or Collect Subject Identification Card

   The investigator or qualified designee will provide the subject with a Subject Identification Card after the subject provides written informed consent. The investigator or qualified designee will retrieve the card from the subject at the last contact (see **Section 9.1.3** for further description of the Subject Identification Card).

3. Record Concomitant Medications

   A record of concomitant medication taken by the subject during the trial is to be obtained.

4. Record (Serious) Adverse Events

   See **Section 7.7.2.4**, for instructions on the assessment and reporting of (Serious) Adverse Events and **Section 7.7.2.5** for instructions on the reporting of (Serious) Adverse Events to the sponsor.

5. Vital Signs

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

6. Body Weight (kg/lbs)

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

7. Physical & Neurological Examinations

   A physical examination including a standard neurological examination will be performed. If the subject is discontinued for any reason during the treatment phase, every attempt should be made to perform a final physical examination.

8. Mini-Mental State Examination (MMSE)

   The MMSE will be administered to the subject in paper form and scored and recorded by the principal investigator or trained designee according to the instructions in the **Manual of Assessments**.

9. Columbia Suicide Severity Rating Scale (C-SSRS)

   The C-SSRS will be administered to the subject and scored and recorded by the principal investigator or trained designee according to the instructions in the **Manual of Assessments**.

The C-SSRS provides a detailed assessment of suicidal ideation and behaviors. The paper version of the C-SSRS will be completed at each visit as indicated in the Trial Flow Chart (and unscheduled visits as clinically indicated). Subjects who at any time during this study spontaneously report AEs of suicidal ideation or behavior with intent (with or without a plan), either as outpatient or during visit interviews, must be assessed by the Investigator and referred for further mental health evaluation as clinically indicated. Subjects who report suicidal ideation with intent, with or without a plan or method (ie, a positive response to Items 4 or 5 in the assessment of suicidal ideation on the C-SSRS) or suicidal behavior must be evaluated that day by a psychiatrist or other trained mental health professional who is a licensed psychologist, social worker or nurse practitioner (or comparable professional qualification in countries outside the United States). Only subjects whose suicidal ideation is passive, who expressly deny any intent to act, and who, after evaluation, are not judged to be at serious risk for self-harm during the course of the trial may continue with trial treatment; others must be discontinued from trial treatment and receive appropriate clinical follow-up care to assure their safety. After appropriate follow-up care, if the investigator judges that the subject can safely resume trial treatment, re-dosing can be considered with Sponsor approval. As part of site validation, sites are to indicate which health care professionals are to be responsible for acute care on-site and to specify referral center(s) to be used for further evaluation. All reports of suicidal ideation or behavior must be recorded as an Event of Clinical Interest (ECI).

10. Neuropsychiatric Inventory (NPI)

    The NPI will be administered to the subject's trial partner/caregiver in paper form and scored and recorded by the principal investigator or trained designee according to the instructions in the **Manual of Assessments**.

11. Review Inclusion/Exclusion Criteria

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

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

    The ADAS-Cog will be administered to the subject in paper form and scored and recorded by the principal investigator or trained designee according to the instructions in the **Manual of Assessments**.

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

    The ADCS-ADL will be administered to the subject's trial partner/caregiver in paper form and scored and recorded by the principal investigator or trained designee according to the instructions in the **Manual of Assessments**.

14. 12-Lead Electrocardiogram (ECG)

    A 12-Lead Electrocardiogram will be performed according to the instructions in a separate **ECG Instruction Manual.**

15. Skin Examinations

To monitor for hypopigmentation, a skin examination will be performed at the visit specified in **Section 2.2**, Trial Flow Chart. The site physician will perform a directed examination of the subject's skin. In addition, sites will instruct subjects to perform a self-examination of their skin between clinic visits (with the assistance of their trial partner, if needed). Subjects should report any abnormal loss of skin pigment to the site. The site physician's examination will focus on exposed skin and any areas of pigment loss noted by the subject or trial partner. If a clinically significant area of hypopigmentation is observed, the site should refer the subject to a dermatologist for further follow-up.

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

1) A clinically significant area of hypopigmentation may include:

a) greater than 3x3 cm

b) a smaller area (eg, 1x1 cm) on the face or hands

c) a speckled pattern involving a larger amount of body surface area or

d) a smaller area (eg, 1x1 cm) of complete pigment loss.

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

2) Clinical judgment criteria include:

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

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

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

16. Laboratory Tests

Laboratory tests for hematology, blood chemistry, and urinalysis are specified in Table 3.

Table 3 Laboratory Tests

Hematology	Chemistry	Urinalysis
Basophils	Albumin	Blood
Eosinophils	Alkaline phosphatase	Glucose
Hematocrit	ALT (SGPT)	Ketones
Hemoglobin	AST (SGOT)	Microscopic exam
Lymphocytes	Bicarbonate	pH
Monocytes	Blood urea nitrogen (BUN)	Protein
Neutrophils	Calcium	Specific gravity
Platelets	Chloride	
RBC	Cholesterol	
WBC	Creatinine	
	Glucose	
	Inorganic phosphorus	
	LDH	
	Potassium	
	Sodium	
	Total Bilirubin	
	Total protein	

EIA=enzyme immunoassay; FTA-ABS=fluorescent treponemal antibody absorption

17. Pharmacokinetic/Pharmacodynamic Blood Samples

Blood samples for PK/PD analyses should be collected, processed, stored, and packaged according to the instructions in the **Laboratory Manual**.

Record the following information for each PK/PD blood sample collected:

- Date and time of each PK/PD blood sample
- Date and time of the last two doses of trial medication before each PK/PD blood sample

Careful attention to the collection, handling, and storage of the PK/PD blood samples is essential to reduce the risk of hemolysis and PK/PD variability. Any deviations from the PK/PD blood collection schedule, such as a missing or breaking a sample, should be documented

18. Clinical Dementia Rating (CDR)

    The CDR will be administered to both the subject and the subject's trial partner/caregiver in paper form, and the CDR Sum of Boxes (CDR-SB) will be scored and recorded by the principal investigator or trained designee according to the instructions in the **Manual of Assessments**.

19. Modified Resource Utilization in Dementia (RUD) Lite Questionnaire

    A modified **RUD Lite** Questionnaire will be administered to the subject's trial partner/caregiver in paper form and recorded by the principal investigator or trained designee according to the instructions in the **Manual of Assessments**.

20. Health Economic Assessment (HEA)

    The **HEA** will be administered to the subject's trial partner/caregiver in paper form and recorded by the principal investigator or trained designee according to the instructions in the **Manual of Assessments**.

21. EuroQol Five Dimension Questionnaire (EQ-5D)

    The EQ-5D will be completed by the subject's trial partner/caregiver in paper form and reviewed by the principal investigator or trained designee according to the instructions in the **Manual of Assessments**.

22. Structural Magnetic Resonance Imaging (MRI)

    Structural MRI for safety monitoring may be conducted at an unscheduled visit if the investigator considers that it is clinically indicated due to an adverse event. Any unscheduled MRI's collected during the long term safety trial should be read by the central reader.

23. Dispense Trial Medication

    The investigator or qualified designee will dispense the subject's treatment kit (see **Section 7.4.1.5.8**) and instruct the subject and subject's trial partner/caregiver regarding dosing with trial medication (see **Section 7.4.1.3.2**).

24. Medication Compliance/Drug Accountability Assessment

    The investigator or qualified designee will account for trial medication as described in **Section 7.4.1.5.8**.

25. Visual Acuity Test

    Visual acuity test will be attempted under standardized conditions according to the MK-8931 BACE Program Manual of Ophthalmic Procedures. Use of the Early Treatment Diabetic Retinopathy Study (ETDRS) chart or equivalent (eg, Landolt 'C' ETDRS chart or Snellen chart) for the test should be attempted first. If cognitive impairment interferes with these tests, Teller Acuity Cards may be attempted to assess visual acuity during the trial. For some subjects, dementia severity may prevent accurate assessment of visual acuity.

26. Posterior Eye Exams

    Posterior eye exam with dilated funduscopy will be performed to assess retinal effects. These procedures will be performed according to the MK-8931 BACE Program Manual of Ophthalmic Procedures.

27. Fundus Photography

    Fundus photography will be performed at the posterior pole of each eye according to the MK-8931 BACE Program Manual of Ophthalmic Procedures. Fundus photographs will be read by a central Reading Center designated by the Sponsor.

28. Fundus Autofluorescence

    Fundus autofluorescence will be measured with a Sponsor-approved instrument according to the MK-8931 BACE Program Manual of Ophthalmic Procedures.

    Autofluorescence pattern changes with enlarged areas of hypo- and hyper-fluorescence will be explored as detailed in the MK-8931 BACE Program Manual of Ophthalmic Procedures.

    Best efforts will be made to accommodate the FAF assessment. Where the FAF assessment is operationally infeasible sites can enroll subjects without the FAF assessment. FAF images will be read by a central Reading Center designated by the Sponsor.

29. Spectral-domain Optical Coherence Tomography (SD-OCT)

    SD-OCT images of the retina will be acquired according to the MK-8931 BACE Program Manual of Ophthalmic Procedures.

[redacted]

7.7 Assessments

7.7.1 Efficacy Assessments

7.7.1.1 Primary Efficacy Endpoints

The primary efficacy endpoints are:

1. the change-from-Baseline score in the ADAS-Cog at Week 104 (Visit 13)
2. the change-from-Baseline score in the ADCS-ADL at Week 104 (Visit 13)

7.7.1.2 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are:

1. the change-from-Baseline score in the ADAS-Cog (at all scheduled timepoints with the exception of Week 104),
2. the change-from-Baseline score in the ADCS-ADL (all scheduled timepoints with the exception of Week 104)
3. the change-from-Baseline score in the CDR-SB (all scheduled timepoints).
4. the change-from-Baseline score in the MMSE (all scheduled timepoints)
5. the change-from-Baseline score in the NPI (all scheduled timepoints)
6. the Health Economics and Quality of Life Endpoints

7. the Pharmacogenetic AnalysesSafety Monitoring and Assessments

7.7.2 Safety Monitoring and Assessments

7.7.2.1 Safety Endpoints

The same safety parameters and AEs designated as being of special interest in the initial 78-week trial will continue to be monitored during the long term safety trial, as follows:1) delirium; and 2) rash ECI (see **Section 7.7.2.2.3**). Some of these AEs are combined into composite endpoints for formal safety analyses (see Table 8).

7.7.2.2 Definition of Terms

7.7.2.2.1 Adverse Event

Per the International Conference on Harmonization (ICH), an adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product. Any worsening (ie, any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

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

Progression of the condition under study is not considered an adverse event unless it is assessed as drug-related by the investigator, or is characterized by unusual or atypical decline for AD progression in the judgment of the investigator, or meets criteria for a serious adverse event (see Section 7.7.2.2.2).

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

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

7.7.2.2.2 Serious Adverse Event

Serious Adverse Event (SAE) is any untoward medical occurrence or effect that at any dose:

1. Results in death;
2. Is life-threatening;
3. Requires hospitalization or prolongation of existing inpatients' hospitalization;
4. Results in persistent or significant disability or incapacity;
5. Is a congenital anomaly or birth defect;
6. Is an Other Important Medical Event.

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

Refer to Table 4 for additional details regarding each of the above criteria.

Life-threatening in the definition of a serious adverse event refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical judgment should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/ reactions that are not immediately life-threatening or do not result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious. These are considered "Other Important Medical Events".

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

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

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

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

7.7.2.2.3 Events of Clinical Interest

An "Event of Clinical Interest" is a non-serious adverse event or occurrence that is designated to be of special interest and must be reported to the sponsor as though it were a serious adverse event – as described in **Section 7.7.2.5.1**.

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

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

The following events are considered events of clinical interest for this trial:

1. An overdose of Sponsor's product, as defined in **Section 7.7.2.2.4**, Overdose, that is not associated with clinical symptoms or abnormal laboratory results is to be reported as a non-serious ECI, using the terminology "accidental or intentional overdose without adverse effect."
2. Adverse events associated with potential for abuse (euphoric mood, mania, hypomania, or similar events; see separate guidance document for details);
3. An elevated AST or ALT lab value that is ≥3 x the upper limit of normal (ULN) and an elevated total bilirubin lab value that is ≥2 x ULN and, at the same time, an alkaline phosphatase lab value that <2 x ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing is to be reported as a non-serious ECI.
4. ALT or AST ≥3 x ULN and a ≥20% increase from baseline;
5. **Incident vasogenic edema in post-treatment MRI scans;
6. **Incident macrohemorrhage in post-treatment MRI scans;
7. **Incident superficial siderosis in post-treatment MRI scans;
8. **Incident microhemorrhage in post-treatment MRI scans;
9. Suicidal ideation or behavior (see separate guidance document for details);

10. Delirium that is ascertained by the investigator or a qualified designee. The Confusion Assessment Method (CAM) should be used to verify delirium whenever feasible [10];
11. A **clinically significant rash** in the investigator's judgment (such as a duration >2 weeks OR a rash that is >10% BSA, OR a rash causes significant discomfort not relieved by topical medication) OR a **severe rash** (as defined in **Section 7.3.3**);
12. Adverse events of clinically significant skin hypo- or depigmentation (see **Section 5.4** for details);

[redacted]

* As determined by the central Reading Center designated by the Sponsor.

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

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

7.7.2.2.4 Overdose

An overdose is a significant variation above the recommended/scheduled dosage for a product. In this current trial an overdose of the investigational product MK-8931 is the administration of at least three times the daily dose of trial medication in a calendar day as specified in **Section 7.4.1.3.2** of this protocol.

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

Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.7.2.2.5 Clinical Supply Complaint

A clinical supply complaint is defined as any communication concerning manufacturing, packaging, labeling or distribution (including adverse storage at depots) of a clinical supply that describes a potential defect related to its identity, strength, quality or purity after it is released and left the control of a Merck-approved packaging facility for distribution. A clinical supply GCP inquiry is defined as any communication of an event taking place at a trial site after the product was satisfactorily received at the trial site, which puts product disposition in question. Examples include adverse storage of product at the trial site and dosing past expiration. Alleged Counterfeit, Diversion and Tampering (CDT), adverse events and trial site errors/issues which do not put product disposition in question should not be reported.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations. This responsibility includes reporting of all clinical supply complaints and/or clinical supply GCP inquiries to the Sponsor.

Clinical supplies complaints and GCP inquiries, as defined above, must be reported to the Sponsor within 1 business day of first becoming aware of the issue. Sponsor contact information and related reporting details can be found in the Investigator Trial File Binder.

7.7.2.2.6 Planned Hospitalization

A hospitalization planned by the subject prior to signing the ICF is considered a therapeutic intervention and not the result of a new SAE and should be recorded as medical history. If the planned hospitalization or procedure is executed as planned, the record in the subject's medical history is considered complete. However, if the event/condition worsens during the trial, it must be reported as an AE.

7.7.2.3 Monitoring

7.7.2.3.1 Monitoring Adverse Events

All adverse events that occur after the consent form is signed but before randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of randomization through 14 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report

forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.7.2.2.2. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

Subjects will be questioned and/or examined by the investigator or a qualified designee for evidence of AEs. The questioning of subjects with regard to the possible occurrence of adverse events will be generalized such as, "How have you been feeling since your last visit?" The presence or absence of specific AEs should not be elicited from subjects. This does not preclude use of other sources of information that may suggest potential AE's (eg. NPI, C-SSRS).

Subjects having AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the investigator.

Adverse events, actions taken as a result of AEs, and follow-up results must be recorded in the electronic Case Report Forms (eCRF; **Section 9.2**), as well as in the subject's source documentation. Follow-up laboratory results should be filed with the subject's source documentation.

For all AEs that require the subject to be discontinued from the trial and SAEs, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate, until final resolution or stabilization of the event(s).

7.7.2.3.2 Monitoring Laboratory Assessments

All laboratory assessments will be performed centrally at a certified laboratory selected by the sponsor. The clinical laboratory values will be reported to the investigator by the laboratory and he/she will review them for significance and consideration as an AE.

7.7.2.4 Assessment of Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in **Table 4**. The investigator's assessment of causality is required for each adverse event. Refer to **Table 4** for instructions in evaluating adverse events.

Table 4 Evaluating Adverse Events

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

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

7.7.2.4.1 Reference Safety Information (RSI) for the Assessment of Expectedness of Adverse Events

The Reference Safety Information (RSI) for assessing the expectedness of an adverse event for the investigational product MK-8931 in this current trial is to be the most recent Investigator's Brochure for MK-8931.

7.7.2.4.2 Potential Toxicities of Investigational Products

Refer to the Investigator's Brochure for additional information on AEs related to toxicities observed to date.

7.7.2.5 Reporting Safety Observations by the Investigator to the Sponsor

7.7.2.5.1 Expedited Reporting

Any occurrence of the following events or outcomes in a subject in the trial must be reported expeditiously by the investigator or qualified designee to the sponsor's Global Safety representative or designee by entering all information relevant to the event in the appropriate eCRFs within **24 hours of learning of the event**. The Global Safety Intake Form – or a sponsor-approved equivalent form – should be used in the event that the EDC system is not functioning.

1. SAE (including SAEs associated with overdose, pregnancy, exposure during pregnancy or lactation);
2. Death;
3. Planned hospitalizations (not previously reported in the medical history);
4. Events of Clinical Interest (ECI);
5. Cancer.

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

Pregnancies and lactations that occur after the consent form is signed but before randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of randomization through 14 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

If the investigator is unsure about when to report an observation from the lists above, the event or outcome should be reported to the sponsor or designee by entering all information relevant to the event in the appropriate eCRFs within 24 hours of learning of the event. The Global Safety Intake Form – or a sponsor-approved equivalent form – should be used in the event that the EDC system is not functioning.

Any observation reported to the sponsor or designee that is also an AE, is to be recorded in the eCRF (**Section 9.2**), as well as in the subject's source documentation, along with any actions taken as a result of AE and follow-up results.

If an autopsy is performed, available results should be entered into the EDC screens.

The investigator must assess causality of the event as relative to the investigational product administered in the trial as described in **Section 7.7.2.4.2**.

7.7.2.5.2 Expedited Reporting by the Sponsor to a Regulatory Health Authority

Global Safety will monitor data for safety. The Sponsor will manage the expedited reporting of relevant safety information to concerned health authorities, competent authorities, and IRBs/IECs in accordance with local laws and regulations.

7.7.2.5.3 Unblinding Treatment for a Subject During the Trial

To assess an occurrence of a safety observation, Global Safety may unblind the treatment of any subject for whom a safety observation was reported by the investigator to the sponsor as described in **Section 7.7.2.5.1**.

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

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

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

7.8 Criteria for Early Termination of the Trial

The trial may be terminated early by the eDMC for safety concerns or based on the results of the interim efficacy analysis for futility of the initial 78-week trial (see **Section 8.2.8**).

8.0 STATISTICAL AND ANALYTICAL PLAN

This section outlines the statistical analysis strategy and procedures for the long term safety trial. Changes to analysis plans made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the trial. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) will be issued for this trial. The statistical analysis of the data obtained from this trial will be the responsibility of the designee from the Clinical Biostatistics Department of the sponsor.

References to either the Screening Visit or the Baseline Visit pertain to the initial 78-week trial. The exact timing of the predose efficacy assessments (screening or baseline) is provided in the Trial Flowchart **(Section 2.2).** Without loss of generality, and within **Section 8** only, a distinction will not be made between the Screening Visit and the Baseline Visit; all predose assessments will be referred to generally as "baseline" assessments. in the event that an assessment was taken at both the Screening Visit and at the Baseline Visit, the data from the Baseline Visit will be used in the analysis.

8.1 Subject Populations to be Analyzed

The analysis populations are the Full Analysis Set population, the Modified Full Analysis Set population and the All-Patients-as-Treated population.

- The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this trial. The FAS population consists of all randomized subjects who have a baseline observation and at least one within-analysis-window (± 6 weeks) post-Randomization observation for the analysis endpoint subsequent to at least one dose of trial treatment. Subjects will be included in the treatment group to which they were randomized. Since the Sponsor's standing internal DMC (siDMC) reviewed unblinded analyses (including the ADAS-Cog) from the first 200 subjects enrolled in the initial 78-week trial, these subjects will be excluded from the FAS population, and hence all efficacy analyses.

  All available observations from the initial 78-week trial will be included in the relevant model-based FAS analyses. Observations from the long term safety trial will be included according to the principles outlined above, with the following additional requirement: the subject must have taken at least one dose of study medication within the 28 days preceding Visit 10B and within the 28 days following Visit 10B.
- The Modified Full Analysis Set (MFAS) population will be utilized for sensitivity analyses and is defined identically to the FAS population with one exception: subjects will be required to have either 1) a baseline measurement for the analysis endpoint or 2) at least one within-analysis-window (± 6 weeks) post-dose, post-randomization observation for the analysis endpoint, but not necessarily both.
- The All-Patients-as-Treated (APaT) population will be used for the analysis of safety data in this trial. The APaT population consists of all randomized subjects who received at least one dose of trial treatment, with subjects included in the treatment group corresponding to the trial treatment they actually received. For most subjects this will be the treatment group to which they were randomized. Subjects who take incorrect trial treatment for the entire treatment period will be included in the treatment group corresponding to the trial treatment actually received. Since the siDMC reviewed unblinded analyses from the first 200 subjects enrolled in the initial 78-week trial, these subjects will be excluded from the primary safety analyses.
- For laboratory, vital sign, and ECG endpoints, at least one postdose measurement is required for inclusion in the analysis of each specific parameter, and a Baseline measurement is required for change-from-Baseline analyses (safety only).

8.2 Efficacy Analyses

Details pertaining to the analysis of all endpoints are discussed below. **Table 5** provides a summary of the Primary Endpoints to be analyzed, as well as the analysis approaches that will be used.

The primary analysis approach will include all efficacy observations in the FAS population, including those obtained after the discontinuation of study medication.

Table 5 Analysis Strategy for Primary Endpoints

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach	Statistical Method[†]	Analysis Population	Missing Data Approach
Primary Endpoints				
Primary Endpoints:				
CFB at Week 104 (Visit 13) in ADAS-Cog score	P	Longitudinal ANCOVA	FAS	Model-based
	S	Longitudinal ANCOVA	FAS	Pattern-Mixture Model (Tipping Point)
	S	Longitudinal ANCOVA (Exclude data collected after the introduction of AChEIs and/or study medication discontinuation)	FAS	Model-based
	S	cLDA	MFAS	Model-Based
CFB at Week 104 (Visit 13) in ADCS-ADL score	P	Longitudinal ANCOVA	FAS	Model-based
	S	Longitudinal ANCOVA	FAS	Pattern-Mixture Model (Tipping Point)
	S	Longitudinal ANCOVA (Exclude data collected after the introduction of AChEIs and/or study medication discontinuation)	FAS	Model-based
	S	cLDA	MFAS	Model-Based

The primary model contains categorical terms for treatment, time, geographic region, gender, APOE genotype, study cohort (from initial 78-week trial), and the interaction of time-by-treatment, with the Baseline values of MMSE, and age included as continuous covariates. Terms for the baseline value and the baseline-by-time interaction of the dependent variable will also be included.

ADAS-Cog=Alzheimer's Disease Assessment Scale Cognitive subscale; ADCS-ADL=Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory; CDR-SB=Clinical Dementia Rating Sum of Boxes; CFB=Change from Baseline; ANCOVA=Analysis of Covariance; cLDA=Constrained Longitudinal Data Analysis; FAS=Full Analysis Set; MMSE=Mini-Mental State Examination; NA=Not Applicable; NPI=Neuropsychiatric Inventory; P=Primary; S=Supportive.

8.2.1 Primary Efficacy Analysis

The primary efficacy endpoints are the change from Baseline (CFB) in ADAS-cog score and the change from Baseline in ADCS-ADL score at Week 104 (Visit 13).

A delayed start design will be used to support the potential disease modifying effect of MK-8931 by comparing the 40mg/40mg arm to the Pbo/40mg arm. However, due to increased variance and anticipated dropout rate over time, the study is not powered to demonstrate significance on these endpoints, even if significance was demonstrated at 18 months.

All available data from the initial 78-week trial will be utilized in the analyses, even that from subjects who do not continue into long term safety trial. It is possible that the 40 mg dose may be dropped for reasons due to safety, in which case all subjects would receive 12 mg. The primary comparison in this case would be between the 12 mg / 12 mg arm and the Pbo / 12 mg arm (with any subjects receiving 40 mg or 60 mg excluded from the analysis).

The primary analysis approach will be conducted separately on each of the endpoints.

A longitudinal ANCOVA model will be used on the change scores, with time treated as a categorical variable so as not to impose any restriction on the trajectory of the means over time. The analysis model will adjust for the categorical factors of geographic region (US/Canada, Europe/Australia/New Zealand, Japan, Rest of the World), treatment (one or two remaining dose[s] of MK-8931 or placebo), gender, APOE genotype (APOE 4 positive, APOE 4 negative), baseline use of Vitamin E (0-400 IU/day, > 400 IU/day), baseline AD medication (use of AChEI or memantine, no use of AChEI or memantine), study cohort from the initial 78-week trial (Safety Cohort, Main Cohort) and the interaction of time-by-treatment, with the baseline values of MMSE and age included as continuous covariates. The baseline value of the dependent variable, as well as the baseline-by-time interaction term will also be included. The Week-78 change-from-Baseline mean treatment differences (MK-8931 – placebo), corresponding confidence intervals (CIs), and P-values will be estimated from this model. An unstructured covariance matrix will be used to model the correlation among repeated measurements.

Three supportive analyses will be conducted on each of the Coprimary Endpoints. These analyses will be conducted to assess the effect of 1) missing data using a pattern-mixture model (“tipping-point” analysis), 2) the use of off-regimen data after the subject has permanently discontinued trial medication or after the subject has initiated AChEIs and 3) analyzing the data using the cLDA model on the MFAS population.

For the first sensitivity analyses (tipping-point), the model-based estimates of the mean treatment difference on the change scores, along with the corresponding confidence intervals and p-values will be provided for a range of *c* values which have been subtracted from the values imputed for the active arms (see 8.2.10) for more details). Of specific interest is the smallest *c* value that, for a given endpoint, transforms a statistically significant result to a non-statistically significant result.

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

For the third sensitivity analysis (cLDA model on the MFAS population), the analysis of the primary efficacy endpoints will be conducted using a constrained longitudinal data analysis (cLDA) method proposed by Liang and Zeger [11]. This model assumes a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. The response vector consists of baseline and the values observed at each post-baseline time point. Additional details pertaining to the cLDA model are included in Section 12.5. The model-based estimates of the mean treatment difference on the change scores, along with the corresponding confidence intervals and p-values will be provided as obtained using the cLDA model, with all of the same covariates that were included in the primary model (now excluding the terms for baseline and baseline-by-time interaction). An unstructured covariance model will be used.

Although the baseline measurement is included in the response vector, it is independent of treatment. Hence, the Baseline means are constrained to be the same for different treatment groups. Note that in the event that there are no missing data, the estimated treatment difference from the above cLDA model will be identical to that from a traditional longitudinal analysis of covariance (ANCOVA) model that uses the Baseline value as a covariate. However, unlike longitudinal ANCOVA, the cLDA model accounts for variability in the baseline values, thus providing more accurate standard errors and CIs for individual treatment effects. Additional details pertaining to the use of the cLDA model in this trial are included in **Appendix 4**.

8.2.2 Multiplicity

As there are no formal hypotheses for the long term safety trial, there is no need for a formal multiplicity strategy. However, 97.51% CIs will be produced for all endpoints with corresponding hypotheses conducted under strong control from the initial 78-week trial, even though formal hypotheses are not defined in this long-term safety trial, and it is acknowledged that strong control is not present.

8.2.3 Exploratory Analyses

It is noted that no supportive analyses (eg, to account for the effect of missing data or protocol violations) will be conducted for any of the exploratory analyses. Basic summary statistics will be provided (mean, standard deviation, quartiles, counts and percentages, as appropriate) by treatment, timepoint, and baseline AD severity (MMSE >20, MMSE $\leq$ 20) for all exploratory endpoints.

8.2.4 Subgroup Analyses

Subgroup analyses will be conducted on ADAS-Cog, ADCS-ADL, NPI, and MMSE at Week 104. The consistency of treatment effect across various subgroups will be assessed through the computation of within-group summary statistics (model-based and as-observed) Further, model-based between-group treatment differences and the corresponding 95% CIs will be constructed for those comparisons (active/active vs. placebo/active), for which both treatment groups within the subgroup level have at least 85 subjects (roughly 15% of subjects randomized). No formal statistical testing of the treatment-by-subgroup interactions will be performed. The following subgroups will be examined:

- Gender (male, female);
- Age (< trial median age, $\geq$ trial median age);
- Race (white, black, Asian, other);
- Randomization Cohort (Safety Cohort, Main Cohort)
- Ethnicity (Hispanic, Not Hispanic);
- Geographic Region (US/Canada, Europe/Australia/New Zealand, Japan, Rest of the World);
- APOE Genotype (APOE 4 positive, APOE 4 negative);
- Disease Severity via MMSE (mild AD: MMSE >20; moderate AD: MMSE $\leq$ 20);
- Trial Completion Status (Completer, Non-completer);
- AD Treatment at Screening (use of AChEI alone, use of memantine alone, use of AChEI and memantine, no use of AChEI or memantine);
- Vitamin E use at Screening (0-400 IU/day, > 400 IU/day)
- Behavioral Symptoms at Baseline (without symptoms NPI = 0, with symptoms NPI > 0);
- Total Hippocampal Volume (AD profile positive, AD profile negative);
- Evidence of Brain Amyloidosis in CSF and/or amyloid PET substudies (positive, negative);
- Highest Education Level (No Undergraduate Degree, Undergraduate Degree or Higher)

Regarding total hippocampal volume, an AD profile will be determined as described in the technical manual. The precise criteria to define an AD profile positive and AD profile negative subjects have not yet been determined but will be selected based on ongoing research at academic sites which is expected to be published before the end of this trial. Similarly, cutoffs for evidence of brain amyloidosis, as measured by CSF and PET, will also be defined based on ongoing studies. All cutoffs will be prespecified prior to the final database lock and will be documented in a memo-to-file.

8.2.5 Parameter Estimates for Primary Endpoints

8.2.5.1 Assumptions for the Effect of MK-8931

Extrapolations out to 24 months (Week 104) were performed on the 18-month (Week 78) parameter assumptions used in the initial 78-week trial and these extrapolations are presented below in **Table 6**.

Table 6 Parameter Assumptions for Progression Rate on Placebo, Standard Deviations, and Within Endpoint Correlations for ADAS-Cog, ADCS-ADL, and CDR-SB

Endpoint	104-Week Placebo/ MK-8931 40 mg Progression Rate	Baseline Standard Deviation	104-Week Standard Deviation	Correlation (Baseline, Week 104)
ADAS-Cog	7.45	7.75	14.97	0.65
ADCS-ADL	-11.73	10.71	20.21	0.61
CDR-SB	2.91	2.28	4.65	0.56

ADAS-Cog=Alzheimer's Disease Assessment Scale Cognitive subscale; ADCS-ADL=Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory; CDR-SB=Clinical Dementia Rating Sum of Boxes

8.2.5.2 Power Calculations

Power calculations for the change-from-baseline treatment difference at 24 months (Week 104) were performed (via simulation) for ADAS-Cog and ADCS-ADL, even though there are no formal hypotheses for these endpoints in the long term safety trial. As shown in **Table 7** both of these hypotheses are underpowered at Week 104, both marginally and when applying an informal sequential testing approach. Specifically, it is possible that formal statistical significance may be observed in the initial 78 week trial (under the prespecified multiplicity approach), while nominal marginal significance (ie, p-value < 0.02495) fails to be observed at Week 104, even if the true underlying effect of MK-8931 continues to increase. This is due to the assumed increased variance and dropout rate over time, with 90% of subjects who complete the base study assumed to continue on into the extension.

Table 7 Power Calculations (MK-8931 40 mg / MK-8931 40 mg vs. Placebo / MK-8931 40 mg)

Marginal Probability†	(%)
ADAS-Cog at Week 104	62.3
ADCS-ADL at Week 104	74.1
ADAS-Cog and **ADCS-ADL** at Week 104	48.0
Sequential Probability	
Success‡ for ADAS-Cog and ADCS-ADL at Week 78 and **ADAS-Cog** at Week 104	58.0
Success‡ for ADAS- Cog and ADCS-ADL at Week 78 and **ADCS-ADL** at Week 104	66.5
Success‡ for ADAS-Cog and ADCS-ADL at Week 78 and **ADAS-Cog** and **ADCS-ADL** at Week 104	46.1
Conditional Probability	
Success‡ for **ADAS-Cog** at Week 104 given success on ADAS-Cog and ADCS-ADL at Week 78	68.4
Success‡ for **ADCS-ADL** at Week 104 given success on ADAS-Cog and ADCS-ADL at Week 78	78.4
Success‡ for **ADAS-Cog and ADCS-ADL** at Week 104 given success on ADAS-Cog and ADCS-ADL at Week 78	54.4

† Marginal power calculations at Week 104 do not require success at Week 78.

‡ 40 mg dose only

Calculations are based on N=1710 randomized (570 subjects/arm) incorporating the assumed dropout rate of 30% at Week 78 and 45% at Week 104.(α = 0.0249).

8.2.6 Dropping Dose Arms

In the event of a dose being dropped, all subjects will receive the remaining active dose.

8.2.7 Accounting for Missing Data

Common reasons for discontinuation from the trial may include lack of efficacy, clinical or laboratory adverse experiences, relocation, withdrawal of consent, protocol violations, and/or data processing issues. Missing data caused by relocation and data processing issues are likely to be missing-completely-at-random (MCAR). On the other hand, missing data caused by discontinuation due to lack of efficacy may be missing-at-random (MAR) because the discontinuation may depend on the observed efficacy outcomes. The MAR or missing-not-at-random (MNAR) mechanisms might each underlie the other reasons to some extent. If treatment in large part determines the loss of data for these other reasons (such as clinical or laboratory adverse experiences), the mechanism may be close to MAR because treatment assignment is an observed variable and included in the analysis model. Based on prior trial results, missing data due to other reasons is relatively infrequent.

No explicit imputation of missing data (beyond the limited imputation performed within an assessment) will be done for the primary analysis approach.

A pattern-mixture model based on the tipping-point approach will be used to assess the robustness of the primary analysis approach. For a given constant, *c*, the tipping point analysis is conducted in a fashion similar to that used in standard multiple imputation[25,26,27], whereby *m* complete datasets are randomly generated using the original observed dataset. These *m* complete datasets are subsequently analyzed using the primary model, and the results of those analyses are then combined. The construction and analysis of these *m* (=50) datasets requires four primary steps:

1) Using a Markov Chain Monte Carlo method[28], make the observed dataset monotone-missing. This will be accomplished for each treatment group using “proc mi“ within SAS 9.3 by utilizing the options “mcmc chain=multiple impute=monotone;”, in conjunction with all of the covariates (excluding treatment) included in the primary analysis model. The random seed will be set equal to 8931017. This step will generate *m* monotone-missing datasets.

2) Applying parametric regression to the monotone-missing datasets, impute the missing values in a stepwise fashion starting with the first postdose timepoint. This will be accomplished for each treatment group using “proc mi“ within SAS 9.3 utilizing the option “monotone reg”, in conjunction with all of the covariates (excluding treatment) included in the primary analysis model. The random seed will be set equal to 8931017. This step will generate *m* complete datasets.

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

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

Using "proc mianalyze" within SAS 9.3, the *m*=50 means and variances from the *m* analyses will be combined to obtain the final test statistic and p-value[25]. The final test statistic $\bar{Q}$ / ($T^{(1/2)}$) is approximately distributed as t_v, where $\bar{Q}$ is the sample mean of the *m* mean estimates, $T=\bar{U} + (m+1)(B/m)$, $\bar{U}$ is the sample mean of the *m* variance estimates, and *B* is the sample variance of the *m* mean estimates. The degrees of freedom, v, will be computed as follows[29], $v = [(v_1)^{-1} + (v_2)^{-1}]^{-1}$, where $v_1 = (m-1)\,[\,1 + (\bar{U}/(1+m^{-1})\,B)]^2$ and $v_2 = (1-\gamma)\,v_0\,(v_0+1)\,/\,(v_0+3)$, with $\gamma = (1+m^{-1})\,B\,/\,T$ and where v_0 represents the complete-data degrees of freedom .

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

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

Handling of Missing Items Within a Clinical Assessment

The final scores of the ADAS-Cog, ADCS-ADL, NPI, MMSE, and CDR-SB are all constructed from multiple subquestions within each assessment. It is possible that one or more subquestions may be missing within each assessment. In this event, the last recorded score for this subquestion(s) may be carried forward from the most recent postdose visit (Last Observation Carried Forward approach). In a similar fashion, missing baseline values may be carried over from the most recent screening visit, if available. Baseline/screening values will never be carried forward to impute missing postdose values. Due to the degenerative properties of AD, with subjects expected to worsen over time, an individual subquestion will not be carried forward for more than one visit. If the same subquestion is missing two visits in a row, then LOCF will be applied to the first missing visit and the subquestion will remain as missing for the second visit (with the total score to then be computed as missing). Further, the total score will be computed as missing if too many

subquestions, prior to applying the LOCF approach, are missing (see endpoint-specific details below). This single imputation approach allows the total score to be calculated using the strength of the other subquestions collected at that time, for that subject. The Sponsor believes this approach to be more accurate than either setting the entire score to missing or to imputing the worst possible score. More complicated missing data approaches are not thought to be warranted, since the amount of missing data within an assessment is expected to be extremely low.

For Baseline ADCS-ADL only (from the initial 78-week trial): Past experience indicates that some subquestions on the ADCS-ADL may mistakenly be omitted at the time of administration. Should this occur at baseline, there will be no opportunity to employ the stated LOCF approach. To avoid a missing total score on the ADCS-ADL (and the subsequent removal of the subject from the primary ADCS-ADL population), the worst possible score for that subquestion will be imputed. Note that this imputation approach will only be implemented for ADCS-ADL (given the relatively small impact of the individual subquestions on the overall score) and only at baseline. A total score will only be computed if the number of missing subtotals is strictly less than three.

Endpoint specific details are as follows:

ADAS-Cog and MMSE: The site will be instructed to enter the worst possible score if the subject is unwilling or unable to answer a subquestion due to reasons related to the area the subquestion is trying to address. If the subject is unable to answer a subquestion for some other reason, then the site will be instructed to leave the subquestion as missing. For both the ADAS-Cog and the MMSE, a total score will be calculated if the original number (prior to applying LOCF) of missing subtotals is strictly less than three.

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

8.2.8 Interim Analysis

Access to Unblinded Reports

The independent eDMC will routinely evaluate unblinded safety analyses of all trial subjects while the initial 78 week trial is blinded. Additional safety analyses may be conducted throughout the trial as requested by the eDMC. The sponsor will be unblinded after completion of the initial 78-week trial.

8.3 Safety Analysis

Subjects from all three arms (40 mg / 40 mg, 12 mg / 12 mg, Pbo / 40 mg) will be included in the safety analyses (with any subject treated with MK-8931 60 mg still excluded from the primary analysis). Where applicable, treatment comparisons will be conducted between the 40 mg / 40 mg and Pbo / 40 mg arms, as well as between the 12 mg / 12 mg and Pbo / 40 mg arms.

The broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, with a drug related AE, with an SAE, with an AE which is both drug-related and serious, or who discontinued because of an AE are considered as Tier 2 endpoints and will be analyzed. Descriptive Safety Endpoints are considered as Tier 3 events and will also be analyzed.

Analyses will be conducted both on the cumulative data including data from the initial 78-week trial as well as this long term safety trial, no analyses will be conducted on the long term safety trial alone.

8.3.1 Analysis of Prespecified Safety Endpoints

The Prespecified Safety Endpoints of 1) microhemorrhage, superficial siderosis or macrohemorrhage in brain MRI scans, 2) vasogenic edema, 3) delirium, and 4) rash ECI are considered as Tier 1 events and will be analyzed as indicated in **Table 8.**

Table 8 Analysis Strategy for Safety Parameters

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

AE=adverse event; CI=confidence interval; ECG=electrocardiogram; PDLC=predefined limit of change; SOC=system organ class; X=results will be provided.

a Adverse experience references refer to both clinical and laboratory AEs. Includes only those endpoints not prespecified as Tier 1 or not already prespecified as Tier 2 endpoints.

8.3.2 Analysis of Commonly Occurring Safety Endpoints

The broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, with a drug-related AE, with an SAE, with an AE which is both drug-related and serious, or who discontinued because of an AE are considered as Tier 2 endpoints and will be analyzed as indicated in Table 8.

8.3.3 Analysis of Descriptive Safety Endpoints

Descriptive Safety Endpoints are considered as Tier 3 events and will be analyzed as indicated in Table 8.

8.4 Trial Medication Compliance and Exposure

8.4.1 Compliance

As part of the routine recording of the amount of trial treatment taken by each subject, the number of pills remaining in trial packaging will be counted and recorded at regular intervals. These results will be used to calculate subject compliance. Instances where the subject took more or less trial medication than prescribed will be recorded on the study medication eCRF. Events that meet criteria for overdose as defined in **Section 7.7.2.2.4** will also be reported as an AE (ECI or SAE, as applicable). To monitor for potential misuse, the site will document significant discrepancies in drug returns where the subject or trial partner returns less trial medication than expected but denies taking extra trial medication (eg, lost or missing medication equivalent to more than one pill per week).

A day within the trial will be considered an “On-Therapy” day if the subject doses on that day. For a subject who is followed for the entire trial period, the “Number of Days Should be on Therapy” is the total number of days from the first dose to the last scheduled day for treatment administration for that subject. For a subject who permanently discontinued trial medication, the “Number of Days Should be on Therapy” is the total number of days from the first dose to the last dose of trial medication.

For each subject, percent compliance will be calculated as 100 times the number of days 'On Therapy" divided by the "Number of Days Should be on Therapy". The average compliance overall, and over each 3-month time frame, will be calculated by treatment group. The percent of subjects who meet various compliance thresholds (eg, 75%, 95% compliant) will also be calculated overall, and over each 3-month time frame, by treatment group. The FAS population will be used for all trial medication compliance calculations.

8.4.2 Exposure

Basic summary statistics for the number of doses of trial medication taken will be calculated overall, and as well as over each 3-month time frame by treatment group. The cumulative percent of subjects taking various numbers of doses of trial medication (eg, one dose, 30 doses) will be calculated by treatment group. The APaT population will be used for all trial medication exposure calculations.

8.5 Demography

Basic summary statistics (means, standard deviations, counts, percentages) will be provided, as applicable, by treatment group, for subject baseline characteristics, subject disposition, and prior and concomitant medication usage.

9.0 ADHERENCE TO ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

The trial must be conducted in accordance with Good Clinical Practice (GCP) as outlined in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines, E6 Good Clinical Practice: Consolidated Guidance and other applicable laws and regulations. In addition, the trial must be conducted in accordance with: (i) the USA Code of Federal Regulations (CFR) if the trial is conducted under a USA IND, regardless of the country involved; (ii) the European Union (EU) Clinical Trial Directive (CTD) and local regulations if the trial is conducted in the EU; and (iii) any specific local regulations if the trial is conducted elsewhere.

9.1 Ethical Conduct of the Trial

9.1.1 Independent Ethics Committee or Institutional Review Board

Prior to initiation of the trial at any site, the trial, including the protocol, informed consent, and other trial documents must be approved by an appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC). The IRB/IEC must be constituted according to applicable regulatory requirements. As appropriate, amendments to the protocol must also be approved by the IRBs/IECs before implementation at the sites, unless warranted to eliminate an immediate hazard. The IRB/IEC approval should be obtained in writing, clearly identifying the trial, the documents reviewed (including informed consent), and the date of the review. The trial as described in the protocol (or amendment), informed consent, and other trial documentation may be implemented only after all the necessary approvals have been obtained and the sponsor has confirmed that it is acceptable for the investigator to do so.

In the event that the IRB/IEC requires changes in the protocol, the sponsor shall be advised and must approve the changes prior to implementation. The investigator shall not modify the trial described in the protocol once finalized and after approval by the IRB/IEC without the prior written approval of sponsor.

In countries where the investigator submits the trial protocol and statement of informed consent to the IRB/IEC, the investigator or qualified designee will forward the approvals to the sponsor.

9.1.2 Subject Information and Consent

The details of the protocol must be provided in written format and discussed with each potential subject, and written informed consent must be obtained for all subjects before any trial-related procedure is performed. Informed consent will be obtained for this trial. NOTE subject participation in this long term safety trial is optional and will only be conducted where approved by local authorities. In obtaining informed consent, the information must be provided in language and terms

understandable to the subject. The subject, or the subject's legal representative, must give their written consent to participate in the trial. The signed and dated consent form itself must be retained by the investigator as part of the trial records. A copy of the signed and dated consent forms must be given to the subject. The consent forms must include all of the required elements of informed consent in accordance with ICH Guidelines E6 and local laws. In addition, the sponsor specifically requests that the consent forms identify it as the sponsor and state that use of the investigational product(s) is experimental and the side effects of the investigational product(s) are not completely known. The consent forms must be approved by the appropriate IRB/IEC and sponsor before trial initiation at a trial site. Any subsequent changes to the approved informed consent forms must be reviewed and approved by the appropriate IRB/IEC and sponsor before implementation.

9.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card after the subject provides written informed consent. The card is to be shown to caregivers in the event of an emergency.

At a minimum, the card must contain the following information:

1. Protocol number;
2. The subject's protocol identification number;
3. A statement identifying the card-carrier as a participant in a clinical trial (eg, "This person is participating in a clinical research trial.");
4. A statement indicating the person might be taking an investigational drug (eg, "This person is taking an experimental drug which could have interactions with other medications, or placebo"); and
5. Contact information in the event of an emergency or hospitalization. The contact information on the card is to be the investigator or a designated site contact, rather than contact from within the sponsor;

The cards may also include other trial-specific information to assist with treatment decisions in the event of an emergency, such as types of concomitant therapies that may, or may not be, permitted as part of emergency treatment. As with any other information provided to subjects, the Subject Identification Card must be approved by the IRB/IEC. Monitors will request that Investigators provide Subject Identification Cards to each subject. Investigators will be asked to request that subjects carry the cards with them while they are participating in the trial.

9.1.4 Registration of the Trial

The trial will be registered by the sponsor on a publicly accessible database. The results will be disclosed by the sponsor on a publicly accessible database.

9.2 Reporting Trial Data to the Sponsor

9.2.1 Data Collection Forms

The Sponsor will provide the site with data collection forms, be they Case Report Forms (CRF), either in paper format or electronic Case Report Forms (eCRF); diaries; Electronic Data Capture (EDC) screens; or other appropriate data collection forms as the trial requires. The investigator is to provide subject data according to the Sponsor's instructions, in the designated data collection form, compliant with GCP practices. The Sponsor will also provide the site with instructions for assisting other parties - such as a central laboratory - to collect data. As instructed by the Sponsor, a designated central laboratory may collect data in a database and provide the completed database to sponsor. All data collection forms and the databases from the trial are the exclusive property of sponsor.

The investigator must maintain records and data during the trial in compliance with all applicable legal and regulatory requirements. Each data point must be supported by a source document at the trial site. Any records or documents used as the source of information (called the "subject source data") are to be retained for review by authorized representatives of the sponsor or a regulatory agency.

The investigator will ensure that there are sufficient time, staff, and facilities available for the duration of the trial to conduct and record the trial as described in the protocol and according to all applicable guidances, laws, and regulations.

All data collection forms (eg, CRFs, diaries; EDC screens), electronic database entries, etc, should be completed as soon as possible after the evaluation has occurred. All dates appearing on the sponsor's subject data collection forms for laboratory tests, cultures, and other data collected, must be the dates on which the specimens were obtained, or the procedures performed.

9.2.2 Preparing Case Report Forms for All Subjects

A CRF must be completed for all subjects who have given informed consent. The Sponsor must not collect subject names, initials, or other personal information that is beyond the scope of the trial from any subject. Subjects are not to be identified by name or initials on the CRF or any trial documents. The only acceptable identification for a subject who may appear on a CRF or trial document is the unique subject identification number. The investigator must maintain contact information for each participant so that all can be quickly contacted by the investigator, if necessary.

All entries into CRFs are the responsibility of the investigator and must be completed by the investigator or a qualified designee. Through signing the Investigator

Signature Page of the protocol the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

9.3 Publications and Other Rights

9.3.1 Rights to Publish by the Investigator

The investigator has the right to publish or publicly present the results of the trial in accordance with this **Section 9.3** of the protocol. In the event that the protocol is a part of a multi-site trial, it is understood that it is the intent of the sponsor and the investigator to initially only publish or present the trial results together with the other sites, unless specific written permission is obtained in advance from the sponsor to publish separate results. The sponsor shall advise as to the implications of timing of any publication in the event clinical trials are still in progress at sites other than the investigator's site.

The investigator agrees not to publish or publicly present any interim results of the trial without the prior written consent of the sponsor. The investigator further agrees to provide to the sponsor 45 days prior to submission for publication or presentation, review copies of abstracts or manuscripts for publication (including, without limitation, slides and texts of oral or other public presentations and texts of any transmission through any electronic media, eg, any computer access system such as the Internet, World Wide Web, etc) that report any results of the trial. The sponsor shall have the right to review and comment with respect to publications, abstracts, slides, and manuscripts and the right to review and comment on the data analysis and presentation with regard to the following concerns:

1. Proprietary information that is protected by the provisions contained in **Section 9.3.2**;
2. The accuracy of the information contained in the publication; and
3. To ensure that the presentation is fairly balanced and in compliance with US FDA regulations.

If the parties disagree concerning the appropriateness of the data analysis and presentation, and/or confidentiality of the sponsor's confidential information, investigator agrees to meet with the sponsor's representatives at the clinical trial site or as otherwise agreed, prior to submission for publication, for the purpose of making good faith efforts to discuss and resolve any such issues or disagreement.

9.3.2 Use of Proprietary or Confidential Information in a Publication

No publication or manuscript shall contain any trade secret information of the sponsor or any proprietary or confidential information of the sponsor and shall be confined to new discoveries and interpretations of scientific fact. If the sponsor believes there is patentable subject matter contained in any publication or

manuscript submitted for review, the sponsor shall promptly identify such subject matter to investigator. If sponsor requests and at sponsor's expense, investigator shall use its best efforts to assist sponsor to file a patent application covering such subject matter with the USA Patent and Trademark Office or through the Patent Cooperation Treaty prior to any publication.

9.3.3 Use of Trial Information in a Publication

Investigator is granted the right subject to the provisions of this protocol to use the results of all work provided by investigator under this protocol, including but not limited to, the results of tests and any raw data and statistical data generated for investigator's own teaching, research, and publication purposes only. Investigator/Institution agrees, on behalf of itself and its employees, officers, trustees, and agents, not to cause said results to be knowingly used for any commercial purpose whatsoever except as authorized by the sponsor in writing.

9.3.4 Authorship of Publications

Authors of publications must meet the International Committee of Medical Journal Editors (ICMJE) guidelines for authorship and must satisfy the 3 criteria that follow:

1. Authors must make substantial contributions to the conception and design of the trial, acquisition of data, or analysis of data and interpretation of results;
2. Authors must draft the publication or, during draft review, provide contributions (data analysis, interpretation, or other important intellectual content) leading to significant revision of the manuscript with agreement by the other authors;
3. Authors must provide written approval of the final draft version of the publication prior to submission.

All contributors who do not meet the 3 criteria for authorship should be listed in an acknowledgments section within the publication, if allowed by the journal, per the ICMJE guidelines for acknowledgment.

9.4 Trial Documents and Records Retention

During the trial and after termination of the trial – including after early termination of the trial – the investigator must maintain copies of all documents and records relating to the conduct of the trial. This documentation includes, but is not limited to, protocols, CRFs and other data collection forms, advertising for subject participation, adverse event reports, subject source data, correspondence with health authorities and IRBs/IECs, consent forms, investigator's curricula vitae/biosketch, monitor visit logs, laboratory reference ranges, and laboratory certification or quality control procedures and laboratory director curriculum vitae. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, or as specified below. The sponsor must be consulted if the investigator wishes to assign the files to someone else, remove them to another location, or is unable to retain them for the specified period.

The investigator must retain trial records for the amount of time specified by applicable laws and regulations. At a minimum, trial records must be retained for the amount of time specified by ICH Guidelines, the EU Good Clinical Practices Directive, or applicable local laws, whichever is longer:

1. The ICH Guidelines specify that records must be retained for a minimum of 2 years after a marketing application for the indication is approved (or not approved) or 2 years after notifying the appropriate regulatory agency that an investigation is discontinued.
2. The European Union (EU) Commission Directive 2003/63/EC which requires that Essential Documents (including Case Report Forms) other than subjects' medical files, are retained for at least fifteen (15) years after completion or discontinuation of the trial, as defined in the protocol.

All trial documents shall be made available if required by relevant health authorities. The investigator should consult with the sponsor prior to discarding trial and/or subject files.

Sponsor will retain all sponsor-required documentation pertaining to the trial for the lifetime of the investigational product. Archived data may be held on microfiche or electronic record, provided that a back-up exists and that a paper copy can be obtained from it, if required.

10.0 INVESTIGATORS AND TRIAL ADMINISTRATIVE STRUCTURE

10.1 Sponsor

The sponsor of this trial is indicated in **Section 1**, Title Page.

10.2 Investigators

10.2.1 Selecting Investigators

Only investigators qualified by training and experience to perform a clinical investigation with MK-8931 are selected. The sponsor will contact and select all investigators (ie, the legally responsible party[ies] at each trial site), who, in turn, will select their staff.

10.2.2 Financial Disclosure Requirement

In connection with the clinical trial described in the protocol, the investigator certifies that, if asked, the investigator will read and answer the Certification/Disclosure Form or equivalent document truthfully and to the best of investigator's ability. Investigator also certifies that, if asked, the investigator will have any other applicable party(s) (eg, subinvestigators) read and answer the Certification/Disclosure Form as a condition of their participation in the trial.

If the financial interests reported on the Certification/Disclosure Form change during the course of the trial or within 1 year after the last subject has completed the trial as specified in the protocol, the investigator and the other applicable party(s) are obligated to inform the sponsor of such financial change.

10.2.3 Clinical Study Report Coordinator Investigator

A Clinical Study Report (CSR) will be prepared by the sponsor or its qualified designee to describe the results of the trial. One of the investigators shall be selected by the sponsor to review the CSR and provide approval of the final CSR in writing. The investigator chosen to review and approve the CSR is to be called the CSR Coordinating Investigator. A second investigator shall be selected as the Alternate CSR Coordinating Investigator. The Alternate CSR Coordinating Investigator is to review and approve the CSR should the first CSR Coordinating Investigator be unable to do so. The sponsor is to select the CSR Coordinating Investigator and Alternate CSR Coordinating Investigator from the investigators using the following criteria:

1. Must be the Principal Investigator at a trial site actively enrolling subjects and participating in the trial;
2. Must be willing and capable of completing the necessary reviews and providing approval of the CSR in writing;

10.3 Central Organizations

Central organizations to be used in the conduct, monitoring and/or evaluation of this trial are provided on the Contact List.

10.3.1 Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

10.3.2 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the eDMC and siDMC regarding the trial.

10.3.3 Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an eDMC will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the eDMC must not be involved with the

trial in any other way (eg, they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

The eDMC will make recommendations to the EOC regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the eDMC will review interim trial results, consider the overall risk and benefit to trial participants (see **Section 8.2.8** - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding responsibilities and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of eDMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the eDMC. The eDMC will monitor the trial at an appropriate frequency, as described in the detailed eDMC charter.

To supplement the routine monitoring outlined in this protocol, the siDMC of the Sponsor will receive unblinded analyses for the first 200 subjects of the 78 week trial only. The siDMC is comprised of members of Sponsor Senior Management, none of whom are directly associated with the conduct of this trial. Specific details regarding responsibilities of the siDMC will be described in a separate charter that is reviewed and approved by the siDMC.

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Appendix 1 Code of Conduct for Clinical Trials

Merck*

Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

D. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC Review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck's Consent Form Review department (U.S. studies) or Clinical Research Director (non-U.S. studies) will approve the subject informed consent form.

B. Safety

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

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

C. Confidentiality

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

D. DNA Research

DNA sequence analyses, including use of archival specimens collected as part of a clinical trial, will only be performed with the specific informed consent of the subject. With IRB approval, an exception to this restriction on use of archival specimens may be possible (for instance, if specimens are de-identified and are not referable to a specific subject).

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

Appendix 2 DNA Sampling and Pharmacogenetic Analysis Procedures

1. **Definitions**
   a. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug response.
   b. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug response.
   c. Genomic Biomarkers: A measurable DNA and/or RNA characteristic that is an indicator of normal biologic processes, pathogenic processes, and/or response to therapeutic or other interventions.
   d. DNA: Deoxyribonucleic acid.
   e. RNA: Ribonucleic acid.
2. **Summary of Procedures for Pharmacogenetics**
   a. Subjects for Enrollment: All subjects enrolled in the current clinical trials will be considered for enrollment.
   b. Consent

      Informed consent for biosamples (ie, DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at an outpatient visit, or during an inpatient stay by the investigator or his or her designate.

      Subjects are not required to participate in the pharmacogenetic sub-study in order to participate in the main trial.
3. **Scope of Pharmacogenetic Study**

   The DNA sample collected in the current trial will be used to study various genetic causes for how subjects may respond to a drug. The DNA sample will be stored to provide a resource for future studies conducted by Merck focused on the study of genes responsible for how a drug enters and is removed by the body, how a drug works, other pathways a drug may interact with, or other aspects of disease. All samples will be used by Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.
4. **Techniques to Collect Samples**

   Blood samples will generally be obtained for all trial participants. Blood samples for both DNA and RNA isolation will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

5. **Confidential Subject Information for Pharmacogenetic Analysis**

Samples will be collected and sent to the laboratory designated for the trial where they will be processed (ie, DNA or RNA extraction, etc) following the Merck approved policies and procedures for sample handling and preparation.

When samples are collected for a specific genotype or expression analysis, this analysis will be detailed in the main body of the clinical protocol (**Section 7.7.3.1**). These samples will be processed, analyzed, and the remainder of the sample will be destroyed. The results of these analyses will be reported along with the other trial results. A separate sample will be obtained from subjects in these protocols for storage in the biorepository for future analyses.

To maintain privacy of information collected from samples obtained for storage and future analysis, Merck has developed secure policies and procedures to maintain subject privacy. At the clinical site, a unique Code will be placed on the blood sample for transfer to the storage facility. The Code is a random number used only to identify the biosample of each subject. No other personal identifiers will appear on the sample tube. The first Code will be replaced with a Sample Code (eg, Genetic Sample Code for DNA sample, Serum Sample code for serum sample) at the Central Laboratory or at the Merck designated facility. This sample is now a single coded sample. The Sample Code is stored separately from all previous sample identifiers. A secure code, hereinafter referred to as a "first coding key", will be utilized to match the Sample Code to the original blood code and subject number to allow clinical information collected during the course of the study to be associated with the biosample. This "first coding key" will be transferred by the central laboratory or Merck designated facility under secure procedures to the Merck group designated as the entrusted keyholder to maintain confidentiality of the biosamples. The Sample Code will be logged into the primary biorepository database, and in this database this identifier will not have identifying demographic data or identifying clinical information (ie, race, sex, age, diagnosis, lab values) associated with it. The sample will be stored in a designated repository site with secure policies and procedures for sample storage and usage.

For DNA samples, a Storage Code will replace the Sample Code at the Merck designated facility. The DNA sample is now a double coded sample. This storage code will be stored separately from all previous sample identifiers. The second secure key referred to as a "second coding key" file will be transferred by the Merck designated facility under secure procedures to the Merck entrusted keyholder. Samples with the second code are sometimes referred to as de-identified samples. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code. Access to both coding keys is needed to link any data or samples back to a subject identifier.

The "keys" could be utilized to reconstruct the link between genetic information and identifiable clinical information, at the time of analysis. This linkage would not be possible for the investigator conducting the analysis, but may only be done by the Merck entrusted keyholder under strict security policies and procedures. The Merck entrusted keyholder will link the information, conduct the analysis, then issue an anonymized data summary on the initially single or double coded samples to the investigator conducting the genetic analysis. The only circumstance by which genetic information would be linked to clinical information would be those situations mandated by health authorities (eg, EMEA, FDA), whereby this information would be directly transferred to the health authority. Once the link between subject's identifiers and the unique codes is deleted, it is no longer possible to trace the data and samples back to individual subjects through the coding keys. Anonymization is intended to prevent subject re-identification.

6. **Biorepository Sample Usage**

Samples obtained for the Merck biorepository will be used for analyses using good scientific practices. Exploratory analyses will not be conducted under highly validated conditions. The scope of research performed on these samples is limited to the investigation of the variability in inherited biomarkers that may correlate with a clinical phenotype in subjects.

Genetic analysis utilizing the DNA samples may be performed by the sponsor, or an additional third party (eg, a university investigator) designated by the sponsor. The investigator conducting the analysis will be provided with a double (single) coded sample. Reassociation of analysis results with corresponding clinical data will only be conducted by the Merck entrusted keyholder. Any contracted third party genetic analysis will conform to the specific genetic analysis outlined in the clinical protocol. DNA sample remaining with the third party vendor after genetic analysis will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

Consent form signed by the subject will be kept under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced to any samples, test results, or medical information once the specimens have been rendered de-identified. Laboratory personnel performing the genetic testing will not have access to the informed consent document, nor will they be able to identify subjects from the double (single) coded specimens. Specimens will be identified to the laboratory only by the Sample double (single) code. Subjects who decline to sign the informed consent document for the sub-study will not have the sample collected or stored, nor will they be discontinued from the main trial unless the pharmacogenetics sample is specifically required for trial enrollment.

A template of each site's informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate sample permissions. The tracking number on this document will be used to assign sample permissions for each sample in the entrusted keyholder's Sample Database.

7. **Withdrawal From the Biorepository and Pharmacogenetic Database**

   Subjects may withdraw their consent to store the blood sample or the DNA or RNA derived from it. Subjects can also request that their sample be destroyed at any time. If samples can be identified in any way (ie, are not anonymized samples), subjects may withdraw consent for banking samples at any time by contacting the investigator responsible for administering their initial informed consent. At that time, subject samples will be removed from the biorepository. Any DNA, RNA, or other biologic samples will be destroyed, destruction will be documented, and sample database information deleted. However, any analyses performed or data obtained from the samples prior to the subject withdrawing consent will not be deleted.

8. **Retention of Data and Biosamples**

   It is anticipated that data generated from processed samples collected during the course this trial will be retained for an indefinite period. DNA specimens will be maintained for potential analysis for 20 years from the acquisition. Samples will be destroyed according to Merck policies and procedures and this destruction will be documented in the repository database.

9. **Data Security**

   Pharmacogenetic and other research databases are accessible only to authorized sponsor and trial administrator research personnel and/or designated collaborators and are only stored and accessible as anonymized data. Database user authentication is highly secure, and is accomplished using network security policies and practices based in international standards (eg, ISO17799) to protect against unauthorized access. The Merck entrusted key holder maintains control over access to all sample data. These data are collected for pharmacogenetic research purposes only as specified in the clinical protocol and will not be used for any other purpose without explicit consent from the research subject.

10. Reporting of Data to Subjects

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to trial participant. Some guidelines advocate a proactive return of data in certain instances.

No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database maintained by Merck on subjects. Principle reasons not to inform or return results to the subject include: lack of relevance of data, limitations of predictive capability of research data, concerns of misinterpretation of data, absence of good clinical practices standards in exploratory research.

If any exploratory results are definitively associated with clinical significance for subjects while the Merck clinical trial is still ongoing, investigators will be contacted with information as to how to offer genetic testing (paid for by Merck) to subjects enrolled and will be advised that genetic counseling should be made available for all who choose to participate.

If any exploratory results are definitively associated with clinical significance after completion of a clinical trial, Merck will publish the results without revealing specific subject information, inform all sites who participated in the Merck clinical trial, and post the anonymized results on our website or other accredited website(s) that allow for public access (eg, Disease-societies who have primary interest in the results) in order that physicians and subjects may pursue genetic testing if they wish to do so.

11. **Gender, Ethnicity, and Minorities**

Although many diagnoses differ in terms of frequency by ethnic population and gender, every effort will be made to recruit all subjects diagnosed and treated on Merck clinical trials for pharmacogenetic sampling. When studies with samples are conducted and subjects identified to serve as controls, every effort will be made to group samples from subjects and controls to represent the ethnic and gender population representative of the disease under current investigation.

12. **Risks Versus Benefits of Pharmacogenetic Testing**

For pharmacogenetic testing, risks to the subject have been minimized. Risks include those associated with venipuncture to obtain the whole blood sample. This sample will be obtained at the time of routine blood samples drawn for clinical reasons.

Data privacy concerns of the subject have been strictly protected against with Merck security, policies and procedures. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

It is necessary for subject-related data (ie, ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc) to be reassociated to double (single) coded samples at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all samples will be stripped of subject identifiers. No information concerning results obtained from genotyping or biomarker studies conducted with samples from the biorepository will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.

13. **Self-Reported Ethnicity**

Subjects who participate in pharmacogenetic study will be asked to provide self-reported ethnicity. Subjects who do not wish to provide this data may still participate in the pharmacogenetic study.

14. **Questions**

Any questions related to the genetic informed consent, genetic sampling, genetic sample handling, or genetic sample storage should be e-mailed directly to PPD

Appendix 3 The National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Criteria for Probable AD[18]

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:

- dementia established by clinical examination and documented by the Mini-Mental Test; Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests;
- deficits in two or more areas of cognition;
- progressive worsening of memory and other cognitive functions;
- no disturbance of consciousness;
- onset between ages 40 and 90, most often after age 65; and
- absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE Alzheimer‘s disease is supported by:

- progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perceptions (agnosia);
- impaired activities of daily living and altered patterns of behavior;
- family history of similar disorders, particularly if confirmed neuropathologically; and
- laboratory results of:
  - normal lumbar puncture as evaluated by standard techniques,
  - normal pattern or non-specific changes in EEG, such as increased slow-wave activity, and
  - evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer‘s disease, after exclusion of causes of dementia other than Alzheimer‘s disease, include:

- plateaus in the course of progression of the illness;
- associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss;

• other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;

• seizures in advanced disease; and

• CT normal for age.

IV. Features that make the diagnosis of PROBABLE Alzheimer‘s disease uncertain or unlikely include:

• sudden, apoplectic onset;

• focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and

• seizures or gait disturbances at the onset or very early in the course of the illness.

Appendix 4 Comparison of the Constrained Longitudinal Data Analysis Model and the Longitudinal ANCOVA Model and Guidance on Longitudinal Data Analysis: *Efficient Use of Baseline Information in Longitudinal Data Analyses*

Comparison of the Constrained Longitudinal Data Analysis Model and the Longitudinal ANCOVA Model

The Constrained Longitudinal Data Analysis (cLDA) model will be used as the primary analysis model in the BACE Phase 2/3 program. This one-page document highlights the relevant differences and similarities between the cLDA model and the traditional longitudinal ANCOVA model. These two models are fully defined and characterized in the attached Merck & Co., Inc. internal technical document "Guidance on Longitudinal Data Analysis: Efficient Use of Baseline Information in Longitudinal Data Analyses". This attached guidance document also provides a fuller explanation of the cLDA model, including additional advantages held by the cLDA model, not listed below, which are not applicable to the BACE program (but nevertheless, provide evidence that the cLDA model is preferred in general over the longitudinal ANCOVA model).

- Both models provide unbiased estimates for their model parameters, resulting in estimates of the treatment difference that are unbiased; this is true for the case of no missing data as well as when the data are missing-at-random (MAR).

- The estimated variance for the treatment difference is unbiased for the cLDA model. On average, the variance for the estimated treatment difference is also unbiased for the longitudinal ANCOVA model.

- The variance of the estimated treatment difference from the cLDA model will not be larger than the average variance from the longitudinal ANCOVA model. However, in most cases the variances from the two models are similar (as confirmed via simulation, see Appendix of the attached).

- The cLDA model provides unbiased standard errors for within-group treatment effects and provides coverage at the appropriate 100(1-α)% level, whereas the longitudinal ANCOVA does not.

- The cLDA model assumes that the underlying population means of all treatments are equal at baseline. It is noted that this assumption need not be verified as it is theoretically known to be true; the only way in which this assumption can be violated is if there is a problem with the blinded randomization to treatment group (a problem which is more severe than unequal baseline means).

Guidance on Longitudinal Data Analysis:

Efficient Use of Baseline Information in Longitudinal Data Analyses

1. Introduction

Measurements are often collected prior to treatment randomization in longitudinal clinical trials. This information can potentially be used for several purposes, including subject selection in studies targeting a study population with a certain disease condition, and as a starting point for measuring the treatment effect in a change from baseline analysis. Comparing treatments in terms of mean change from baseline is common in many longitudinal clinical trials. When there is only one post-randomization measure, treatment effects on mean change from baseline are often assessed using an analysis of covariance (ANCOVA) model with the baseline value as a covariate and either the post-baseline value or the calculated change from baseline value as the dependent variable; throughout this document, without loss of generality, we assume that the dependent variable is the change from baseline for ANCOVA-based analyses. Estimates and statistical tests from an ANCOVA model conditional on baseline values are unbiased under an assumption of normality [1]. When the baseline measurement is correlated with the post-baseline measurement, adjusting for baseline using ANCOVA has been shown to remove conditional bias in treatment group comparisons due to chance imbalances [2], and to improve efficiency over unadjusted comparisons [3].

With several post-randomization measurements (repeated measures over time), a longitudinal data analysis (LDA) model can be used, in which the change from baseline is calculated at each post-randomization time point and the baseline measurement is included as a covariate in the model. This model will hereafter be referred to as the Longitudinal ANCOVA model. Alternatively, a full likelihood approach can be used. First proposed by Liang and Zeger [4], in the full likelihood LDA model the baseline value is included as a dependent variable in the response vector, along with the post-baseline values. Of note, in the Longitudinal ANCOVA model, the baseline mean responses for each treatment group are implicitly assumed equal, which is reasonable due to randomization. A similar "constraint" can also be imposed in the full likelihood LDA model; the constrained full likelihood LDA model will hereafter be referred to interchangeably simply as the LDA model.

While both the Longitudinal ANCOVA and LDA models produce identical point estimates for the treatment effect in simple models that adjust for [categorical] time when no data are missing, estimates of standard errors for within-group mean changes from baseline from the LDA (but not the Longitudinal ANCOVA) model account for the variability of the baseline measurements. In addition, the LDA model does not exclude from the analysis post-randomization values for subjects with missing baseline values, leading to more efficient use of all the data.

A comprehensive review of late-stage clinical trials at Merck revealed inconsistencies and inefficiencies in methods being used for the analysis of longitudinal data among various therapeutic areas. This guidance document, produced by the Longitudinal Data Analysis Working Group of the Early/Late-stage Statistical Technical Issues Committee (ELSTIC), is intended to remove unnecessary disparities across BARDS sites for addressing analyses of mean change from baseline by recommending an efficient and statistically sound default strategy with supporting rationale.

The recommendation is to **use the full likelihood LDA model proposed by Liang and Zeger [4] as the default strategy for comparing treatments in terms of mean change from baseline in longitudinal clinical trials [5]. This LDA model will include baseline as one of the repeated measures with a constraint of equal mean across randomized groups at baseline, and use Kenward-Roger adjustment [6] with REML approach and an unstructured covariance [7].**

Table 1 provides a summary of the reasons for recommending the LDA over the Longitudinal ANCOVA model. When there are no missing data, the Longitudinal ANCOVA and the LDA models are generally comparable with respect to treatment group comparisons. However, in the presence of missing baseline data, the LDA model has superior power to detect treatment differences. Moreover, in both cases (missing or no missing data), confidence intervals for the least square means (LSMEANS) of the individual treatment groups are not covered at the appropriate 100(1-α)% level in the Longitudinal ANCOVA model, or in any model that uses baseline as a covariate. Note that this limitation also exists in the special case where there is only 1 post-baseline time point. As such, the recommendation is to use the LDA model in lieu of the standard ANCOVA model even when there is only one post-baseline time point. This recommendation also holds whether or not stratification factors are being adjusted for in the model.

Table 1
Advantages of the full likelihood LDA versus Longitudinal ANCOVA

Issue	Advantage of the LDA model
1) Missing baseline data.	The LDA model provides more efficient between-group comparisons because, unlike the Longitudinal ANCOVA model, it includes subjects who are missing a baseline measurement but have at least one post-baseline measurement.
2) Variability estimate for designing future trials.	The LDA model provides unbiased standard errors for within-group treatment effects, whereas the longitudinal ANCOVA model underestimates the variance.
3) Coverage of within-group confidence intervals for mean change from baseline.	The LDA model provides coverage at the appropriate 100(1-α)% level (under normality), whereas the Longitudinal ANCOVA model does not.
4) Subjects missing all post-baseline measurements.	The LDA model includes baseline measurements of such subjects in the analysis, whereas the Longitudinal ANCOVA model does not. If the probability of missing a post-baseline measurement depends on the magnitude of the baseline measurement (missing at random), then the LDA model will yield unbiased result but the Longitudinal ANCOVA model will not.
5) Implicit modeling assumptions regarding baseline means in models that adjust for stratification and stratification by time interaction.	The LDA model provides more flexibility and is less restrictive than the Longitudinal ANCOVA model. For example, a standard implementation of the latter implicitly (and often, erroneously) assumes that the baseline mean is the same for all strata. Moreover, the LDA model can more easily accommodate user-specified weights for the different strata for estimating and testing treatment effects.
6) Implicit modeling assumptions regarding correlation between baseline and post-baseline measurements in models that adjust for stratification and stratification by time interaction.	The Longitudinal ANCOVA model implicitly (and often, erroneously) assumes that the correlation between baseline and each post-baseline measurement is the same for all levels of the stratification factor. The LDA model does not make this restrictive assumption.

If the parameter of interest is the mean *percent change from baseline* rather than the mean change from baseline, then the following two options may be considered: (1) Use the LDA model in which the longitudinal response vector includes the baseline measurement and the calculated post-baseline percent change from baseline measurements; (2) Use the LDA model in which the longitudinal response vector includes the log-transformed baseline and post-baseline measurements, and then use the delta method, or any other appropriate method (eg, see [8]), to get point estimates and standard errors on the original measurement scale.

Of note, ignoring baseline values in the analysis is not recommended in general, unless baseline values are non-informative or confounded with covariates included in the analysis (eg, a categorical baseline severity variable).

A detailed description of the rationale for recommending use of the LDA model, along with suggestions on appropriate implementation and template language for the Data Analysis Section (DAS) of a clinical protocol, is provided in the sections that follow.

2. Longitudinal data analysis methods for comparing treatments in terms of mean change from baseline

Sections 2 through 5 consider models to compare treatments in terms of mean change from baseline while adjusting for time as a categorical factor in the model. Adjusting for additional variables (eg, stratification factors) is considered in Section 6.

2.1 Longitudinal ANCOVA model

Suppose responses are measured at baseline ($T = 0$) and at T post-baseline time points in a clinical trial. Let Y_{ijt} be the response for subject i, with treatment assignment j, at time t. The marginal mean of the change from baseline, conditional on baseline Y_{ij0}, at time t can be modeled as:

$$E(Y_{ijt}^* \mid Y_{ij0}) = \alpha_t Y_{ij0} + \beta_{jt} I(treatment = j) I(time = t), \quad t = 1, 2, \ldots, T,$$

where $Y_{ijt}^* = Y_{ijt} - Y_{ij0}$ is the change from baseline value at time t. The slope, α_t, can be different for each time t and β_{jt} is the effect for treatment j at time t after adjusting for the baseline effect. The standard analysis using this model assumes that post-baseline values are multivariate normally distributed. The model conditions on a subject's baseline value. As such, the baseline is treated as fixed (rather than as a random variable) in the analysis, and subjects with missing baseline values are excluded. This model corresponds to the commonly used ANCOVA model for a pre-post study design when $T = 1$.

With repeated measures (ie, $T > 1$), a covariance matrix can be specified in the mixed model to account for within subject correlation at times $t > 0$. A separate covariance matrix can be specified for each treatment group; however, because the baseline value is not part of the response vector, the correlation between baseline and each post-baseline measurement in the ANCOVA model is implicitly assumed to be the same for each treatment group. For convenience, we focus on

the last time point ($t = T$) and assume the study has two arms, a test drug ($j = 1$) and a control ($j = 0$). The comparison of interest is the treatment effect on the change from baseline at the last time point:

$$\theta_T = \beta_{1T} - \beta_{0T}.$$

The change from baseline LSMEANS for test drug and control are estimated as:

$$\hat{\theta}_{1T} = \hat{\alpha}_T \tilde{Y}_{\bullet\bullet 0} + \hat{\beta}_{1T} \text{ and } \hat{\theta}_{0T} = \hat{\alpha}_T \tilde{Y}_{\bullet\bullet 0} + \hat{\beta}_{0T},$$

respectively, where $\tilde{Y}_{\bullet\bullet 0}$ is the overall mean at baseline of all subjects included in the analysis.

2.2 LDA model

Utilizing the same notation, the LDA model includes the baseline value as part of the response vector. The marginal mean responses can be modeled as:

$$E(Y_{ijt}) = \gamma_0 + \gamma_{jt} I(treatment = j) I(time = t \text{ and } t > 0), \quad t = 0,1,2,\ldots,T,$$

where γ_0 is the mean response at $t = 0$, which is constrained to be the same for both treatment groups due to randomization, γ_{jt} is the effect for treatment j at time t. The LDA model assumes that baseline and post-baseline values are jointly multivariate normally distributed. A covariance matrix can be specified in the mixed model to account for within subject correlation at times $t \geq 0$ (including baseline). Unlike the ANCOVA model, when a separate covariance matrix is specified for each treatment group the correlation between baseline and each post-baseline measurement is not assumed to be the same for each treatment group.

The treatment effect on the change from baseline at the last time point is estimated from this model as:

$$\eta_T = \gamma_{1T} - \gamma_{0T}.$$

The change from baseline LSMEANS for test drug and control are estimated as:

$\hat{\gamma}_{1T}$ and $\hat{\gamma}_{0T}$, respectively.

3. Comparing the Longitudinal ANCOVA and LDA models

3.1 Treatment difference estimates

Under the Longitudinal ANCOVA model, the treatment difference is the conditional mean difference between treatment groups:

$$\theta_T = \beta_{1T} - \beta_{0T} = E(Y_{i1T}^* - Y_{i0T}^* \mid Y_0) = E(Y_{i1T} - Y_{i0T} \mid Y_0).$$

Using conditional expectation, it can be seen that

$$\eta_T = \gamma_{1T} - \gamma_{0T} = E(Y_{i1T} - Y_{i0T}) = \theta_T.$$

Both models provide unbiased estimates for their parameters, resulting in estimates of the treatment difference that are unbiased; this is true for the case of no missing data, and when data are missing at random (MAR). Furthermore, baseline means are assumed equal for the test drug and control groups in both models. Therefore, the resulting treatment difference estimate for both models is the expectation of the response difference between groups under the constraint of common baseline mean.

The overall variance of the estimated treatment difference, $Var(\hat{\theta}_T)$, can be determined using the conditional variance formula:

$$Var(\hat{\theta}_T) = E(Var(\hat{\theta}_T \mid Y_0)) + Var(E(\hat{\theta}_T \mid Y_0))$$

where $Var(\hat{\theta}_T \mid Y_0)$ is the variance estimated from the Longitudinal ANCOVA model. The second term on the right hand side of the equation is zero since $E(\hat{\theta}_T \mid Y_0) = E(\hat{\beta}_{1T} \mid Y_0) - E(\hat{\beta}_{0T} \mid Y_0) = \beta_{1T} - \beta_{0T}$ is constant. Therefore,

$$Var(\hat{\theta}_T) = E(Var(\hat{\theta}_T \mid Y_0)).$$

As such, on average, the variance for the estimated treatment difference is unbiased from the longitudinal ANCOVA model. This was confirmed empirically through simulations (see Appendix).

Under the LDA model, the estimated variance for the treatment difference estimate is unconditional. The variance estimate is based on REML and unbiased under the model assumption. It can be shown that

$$Var(\hat{\eta}_T) = Var(E_{Y_0}(\hat{\theta}_T)) \le E_{Y_0}(Var(\hat{\theta}_T \mid Y_0)) = Var(\hat{\theta}_T).$$

Therefore, the variance of the estimated treatment difference from the LDA model will not be larger than the average variance from the longitudinal ANCOVA. When there are no missing data, the point estimate of the treatment difference is identical. This implies that the LDA model will be at least powerful as the longitudinal ANCOVA for the treatment comparisons. In most of the cases, the variances from these two models are fairly similar though. This was also confirmed through simulations (see Appendix).

3.2 LSMEAN estimates

Under the Longitudinal ANCOVA model, the LSMEAN for individual treatment groups is defined as:

$$\hat{\theta}_{jT} = \hat{\alpha}_T Y_{\bullet\bullet 0} + \hat{\beta}_{jT} .$$

When there are no missing data, the baseline slope coefficient can be estimated as:

$$\hat{\alpha}_T = \frac{\sum_i \sum_j (y_{ijT} - y_{\bullet jT})(y_{ij0} - y_{\bullet j0})}{\sum_i \sum_j (y_{ij0} - y_{\bullet j0})^2} - 1$$

and

$$E(\hat{\alpha}_T) = \rho(\sigma_T / \sigma_0) - 1$$

where σ_T and σ_0 are the standard deviations of the responses at time T and baseline, respectively. In general, the parameter estimates for α_T, β_{1T} and β_{0T} are asymptotically unbiased under MAR. In fact, the change from baseline LSMEAN for each treatment group estimates the expected difference between response at time T and baseline for that group:

$$E(\hat{\theta}_{jT}) = E[E(\hat{\alpha}_T \tilde{Y}_{\bullet\bullet 0} + \hat{\beta}_{jT} \mid Y_0)] = \alpha_T E[\tilde{Y}_{\bullet\bullet 0}] + \beta_{jT} = E(Y_{ijT} - Y_{ij0}) .$$

The last equality uses that the expected baseline means are the same across the subjects due to randomization.

However, the conditional variance estimate of $\hat{\theta}_{jT}$, $Var(\hat{\theta}_{jT} \mid Y_0)$, obtained from the Longitudinal ANCOVA model may incorrectly estimate the overall variance of $\hat{\theta}_{jT}$. Using the conditional variance formula, we have:

$$\begin{aligned} Var(\hat{\theta}_{jT}) &= E[Var(\hat{\theta}_{jT} \mid Y_0)] + Var[(\rho\sigma_T/\sigma_0 - 1)Y_{\bullet\bullet 0} + \beta_{jT}] \\ &= E[Var(\hat{\theta}_{jT} \mid Y_0)] + (\rho\sigma_T/\sigma_0 - 1)^2\sigma_0^2/N \end{aligned}$$

where N is the total sample size used in calculating the baseline mean. To illustrate the issue, assume equal allocation between treatment groups, no missing data and the same measurement variances over time (ie, $\sigma_T^2 = \sigma_0^2$). Under these assumptions, the residual variance for the Longitudinal ANCOVA model conditional on the baseline is $(\sigma_0^2(1-\rho^2))$, resulting in $E[Var(\hat{\theta}_{jT} \mid Y_0)] = c(\sigma_0^2(1-\rho^2)/N$, where c is a constant independent of σ_0^2 and N. This reduces $Var(\hat{\theta}_{jT})$ to:

$$\begin{aligned} Var(\hat{\theta}_{jT}) &\approx E[Var(\hat{\theta}_{jT} \mid Y_0)] + (\rho - 1)^2\sigma_0^2/N \\ &\approx E[Var(\hat{\theta}_{jT} \mid Y_0)][1 + (\rho - 1)^2/\{c(1-\rho^2)\}] \\ &\approx E[Var(\hat{\theta}_{jT} \mid Y_0)][1 + (1-\rho)/\{c(1+\rho)\}] \end{aligned}$$

Therefore, the estimated variance of the change from baseline LSMEAN obtained from the Longitudinal ANCOVA approach ($Var(\hat{\theta}_{jT} \mid Y_0)$) underestimates the overall variance of $\hat{\theta}_{jT}$. The relative amount of underestimation is proportional to $((1-\rho)/((1+\rho))$. It is more extreme when the correlation between baseline and the response at time T is small or negative, and less extreme when the correlation is close to 1. The relative underestimation does not decrease with increasing sample size, as confirmed through simulation (see Appendix).

Note that the above derivation holds asymptotically when there are missing data because the restricted maximum likelihood (REML) estimates are asymptotically unbiased for all parameters, as long as the data are missing at random. If there are subjects who have an observed baseline value but all post-baseline values are missing, and the missing data depends on the baseline value, then the MAR condition is no longer satisfied when these subjects are excluded from the analysis model. As such, the Longitudinal ANCOVA model may produce biased LSMEAN estimates.

For the full likelihood LDA model, the parameter estimates are unconditional. All subjects with available data either at baseline or post-baseline are included in the analysis. Inference based on maximum likelihood is valid, as long as the data are missing at random. Therefore, there are no bias or variance underestimation issues for the LDA model.

3.3 Normality assumption

The Longitudinal ANCOVA model assumes that the post-baseline measurements are multivariate normally distributed, while the LDA model assumes that the baseline and post-baseline measurements are jointly multivariate normally distributed. The robustness of both models to deviations from normality was assessed via simulation (see Appendix). Both models were robust to mild departures from normality, but were generally inefficient under more severe departures from normality. As such, robust parametric or non-parametric alternatives to the REML-based analysis of the LDA model may be more appropriate if a considerable departure from normality is suspected; users should refer to the Guidance for Analysis of Continuous Non-normal Longitudinal Data for further details.

4. Longitudinal data analysis methods for an endpoint calculated from baseline in a non-linear form

When baseline is used to calculate a dependent variable of a non-linear form, the LDA model can still be used. For example, if the parameter of interest is the mean *percent change from baseline* rather than the mean change from baseline, then the following two options may be considered: (1) Use the LDA model in which the longitudinal response vector includes the baseline measurement and the calculated post-baseline percent change from baseline measurements; (2) Use the LDA model in which the longitudinal response vector includes the log-transformed baseline and post-baseline measurements, and then use the delta method, or any other appropriate method (eg, see [8]), to get point estimates and standard errors on the original measurement scale.

5. Issues with SAS MIXED procedure for LSMEAN estimates

When the SAS MIXED procedure is used to fit a longitudinal ANCOVA model with repeated measures and missing data, the default LSMEAN estimates may not be appropriate. For a given treatment group, the individual treatment group LSMEANS should be:

$$\hat{\theta}_{jT} = \hat{\alpha}_T \tilde{Y}_{\bullet\bullet 0} + \hat{\beta}_{jT}$$

where $Y_{\bullet\bullet 0}$ is the mean response at baseline of all subjects in the analysis population. The default in the SAS MIXED procedure is to calculate the baseline mean from the analysis dataset. When data are missing, some subjects have fewer observations in the analysis dataset. As a result, the default baseline mean is a weighted average of baseline values across subjects, where the weight is proportional to the number of observations in the analysis dataset for a given subject. Under MAR, the weighted baseline mean may be biased.

To fix this problem, the baseline mean should be calculated outside of the SAS MIXED procedure, using one baseline observation per subject. This calculated mean can be used in the LSMEAN statement with the AT =option or in the ESTIMATE statement.

When the model is more complicated (adjustment for other factors), the ESTIMATE statement provides more flexibility.

6. Stratification

Adjustments for stratification factors (such as study center, gender, etc.) do not pose any additional theoretical difficulties, although assumptions between models that appear similar can be different. For example, adding a stratification and stratification by time interaction to the Longitudinal ANCOVA model defined in Section 2.1 implicitly makes several assumptions, including that (1) the correlation between baseline and post-baseline measurements is the same for each level of the stratification variable; and (2) the baseline means are the same for each level of the stratification factor. The LSMEAN estimates are calculated in SAS using this common mean. In contrast, an LDA model with the additional stratification and stratification by time factors does not impose the same implicit assumptions. As a result, estimates from the two models will not be the same, even when there are no missing data. An LDA model can be constructed that imposes the same implicit assumptions as the Longitudinal ANCOVA model when adjusting for additional stratification factors, although in most situations the less restrictive assumptions of the LDA model may make more sense.

7. REML and Kenward-Roger adjustment

Restricted (or residual) maximum likelihood (REML) is the default estimation method for the covariance parameters in SAS PROC MIXED. It is a particular form of the maximum likelihood applied to linear functions of **Y**, say **KY**, for which **K** is specifically designed so that **KY** contains none of the fixed effects which are part of the model for **Y**. Let $\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}$. Then **K** is any matrix with row rank n – rank(**X**) satisfying $\mathbf{KX} = \mathbf{0}$. As a result, variance components are estimated without being affected by the fixed effects, $\boldsymbol{\beta}$, and, in estimating variance components, degrees of freedom for the fixed effects are taken into account implicitly [9]. In contrast, the conventional maximum likelihood based on the full set of observations generally underestimates the variance components. Therefore, REML is the recommended estimation method for the covariance parameters.

By default, the variance for the fixed effects estimate, $\text{var}(\hat{\beta}) = (X'V^{-1}X)^{-1}$, is estimated by plugging in the REML estimates of the covariance parameters, $\hat{\text{var}}(\hat{\beta}) = (X'\hat{V}^{-1}X)^{-1}$. This underestimates the true variability of $\hat{\beta}$ as the uncertainty associated with the estimation of the covariance parameters is not taken into account. In addition, statistical inference for a linear combination of the fixed effects, H: $\mathbf{L}\boldsymbol{\beta} = \mathbf{0}$, is often based on the general t-statistic, $t = L\hat{\beta} / \sqrt{L(X'\hat{V}^{-1}X)^{-1}L'}$, which, in general, is only approximately t-distributed, and its degrees of freedom must be estimated. The default method for degrees of freedom in SAS PROC MIXED procedure is the "between-within" approach [??], which does not have good statistical properties when there are missing data. It is recommended to use DDFM=KR option in the MODEL statement of SAS PROC MIXED, which first adjusts the estimated variance for $\hat{\beta}$ and then computes Satterthwaite-type degrees of freedom [6]. It is shown that the adjusted variance estimate and corresponding degrees-of-freedom provide better statistical properties, especially for studies with small sample sizes.

8. Assessing the Recommendation Using Simulations

Results from an extensive simulation study (see Appendix) empirically confirm the more desirable properties of the LDA model presented in this guidance. The simulation study compared the LDA model to the Longitudinal ANCOVA model under a variety of scenarios when considering treatment and time factors in the model. As noted in Section 6, adjustments for additional stratification factors do not pose any additional theoretical difficulties, although consideration for the assumptions in Longitudinal ANCOVA model versus the LDA model may warrant some attention. When both models contain the same constraints for the stratification factor(s) and baseline means, the more desirable properties of the LDA model hold.

It is worth noting that the constraint (mean baseline responses are the same for both treatment groups) implicitly assumed in the Longitudinal ANCOVA model does not have to be assumed in the LDA model, but it makes sense in the context of randomized clinical trials where proper randomization ensures that the assumption is true. When the assumption is true, the LDA model with the constraint will adjust for observed chance imbalances in baseline measurements between treatment groups and increase efficiency of treatment group comparisons [2, 3].

Results from a separate simulation study also empirically confirm the more desirable properties of the Kenward-Roger adjustment. The simulation study compared three methods for computing the denominator degrees of freedom for the tests of fixed effects: the between-within method, the Satterthwaite approximation, and the Kenward-Roger adjustment.

9. Implementing the Recommendation using SAS

The SAS code required to fit the LDA model for analyses in terms of change from baseline is provided in this section. For illustration, assume that there is 1 baseline and 3 post-baseline measurements for each subject, and a stratification variable that has 3 levels. The data take the form:

Subj	Strata	Trt	time	Y	cy	Bl
PPD	1	1	0	5.25664	0.00000	5.25664
	1	1	1	4.65575	-0.60089	5.25664
	1	1	2	2.58320	-2.67344	5.25664
	1	1	3	1.16863	-4.08801	5.25664
	2	1	0	4.27706	0.00000	4.27706
	2	1	1	2.79553	-1.48153	4.27706
	2	1	2	1.85245	-2.42461	4.27706
	2	1	3	0.69176	-3.58530	4.27706
	3	1	0	4.59872	0.00000	4.59872
	3	1	1	3.69201	-0.90671	4.59872
	3	1	2	2.71452	-1.88420	4.59872
	3	1	3	1.52998	-3.06874	4.59872
	⋮	⋮	⋮	⋮	⋮	⋮
	1	2	0	5.69308	0.00000	5.69308
	1	2	1	3.44989	-2.24319	5.69308
	1	2	2	5.40212	-0.29096	5.69308
	1	2	3	3.12272	-2.57036	5.69308
	2	2	0	4.30366	0.00000	4.30366
	2	2	1	3.12098	-1.18268	4.30366
	2	2	2	3.16588	-1.13778	4.30366
	2	2	3	2.79032	-1.51334	4.30366
	3	2	0	4.48876	0.00000	4.48876
	3	2	1	3.14964	-1.33912	4.48876
	3	2	2	2.71894	-1.76982	4.48876
	3	2	3	2.37974	-2.10902	4.48876
	⋮	⋮	⋮	⋮	⋮	⋮

9.1 Fitting the LDA model in SAS without adjusting for stratification variables

The LDA model described in Section 2.2 of the guidance document can be fit within SAS using the following code:

```
*****************************************************************
**;
** data step necessary prior to running SAS PROC MIXED;
*****************************************************************
**;
DATA long; SET long;
    ARRAY T{4} t0-t3; * time indicator variables;
    ARRAY TT{4} tt0-tt3; * time by treatment 1 (vaccine) indicator variables;
    ** define week times treatment 1 indicator variables;
    DO i = 1 TO 4;
        t{i} = (time=(i-1));
        tt{i} = t{i}*(trt=1);
    END;
    DROP i;
RUN;

*****************************************************************
**;
** LDA model fit in SAS PROC MIXED;
*****************************************************************
**;
PROC MIXED DATA=long;
    CLASS subj time;
    MODEL y=time tt1 tt2 tt3/ddfm=KR;
    REPEATED time / SUBJECT=subj TYPE=UN;
    ESTIMATE 'T1 Diff (V-P)' tt1 1;
    ESTIMATE 'T2 Diff (V-P)' tt2 1;
    ESTIMATE 'T3 Diff (V-P)' tt3 1;
    ESTIMATE 'T1 Placebo LSM' time -1 1 0 0;
    ESTIMATE 'T2 Placebo LSM' time -1 0 1 0;
    ESTIMATE 'T3 Placebo LSM' time -1 0 0 1;
    ESTIMATE 'T1 Vaccine LSM' time -1 1 0 0 tt1 1;
    ESTIMATE 'T2 Vaccine LSM' time -1 0 1 0 tt2 1;
    ESTIMATE 'T3 Vaccine LSM' time -1 0 0 1 tt3 1;
    ODS OUTPUT Estimates=outm1;
RUN;
```

The corresponding Longitudinal ANCOVA model can be fit within SAS using the following code:

```
**********************************************************************
**;
** Longitudinal ANCOVA model fit in SAS PROC MIXED;
**********************************************************************
**;
PROC SQL NOPRINT;
    SELECT mean(y) INTO: bb
    FROM long WHERE time=0;
QUIT;
PROC MIXED DATA=long;
    WHERE time>0;
    CLASS subj time trt;
    MODEL cy = bl trt time trt*time bl*time/ddfm=KR;
    REPEATED time / SUBJECT=subj TYPE=UN;
    LSMEANS trt trt*time / pdiff at bl=&bb;
    ODS OUTPUT LSMeans=outm2a Diffs=outm2b;
RUN;
```

Of note, the baseline by time interaction term is included in the Longitudinal ANCOVA model for consistency in the modeling assumptions. If this interaction term is removed in the Longitudinal ANCOVA model, the correlation of the baseline measurement to each post-baseline measurement is assumed constant (even when specifying an unstructured correlation matrix). The LDA model does not make this assumption. If in reality there is no baseline by time interaction, enforcing the assumption of different correlations between the baseline measurement and each post-baseline measurement may result in a minor efficiency loss. Given the sample sizes of most clinical trials, there is no material effect on the efficiency of the analysis. However, if there really is such an interaction, leaving it out could potentially lead to more bias.

Also of note, a typical exploratory analysis in the analyses of longitudinal data is to refit the Longitudinal ANCOVA model defined in Section 2.1 with a baseline by treatment interaction, in order to assess whether the treatment effect is consistent across varying baseline values. A similar test cannot be performed using the LDA model since the baseline measurement is part of the response vector. As an exploratory analysis, the need for a formal test (and p-value) is open to discussion. If required, a baseline by treatment interaction can be explored using the LDA model after creating a categorical baseline variable and adjusting for it in the model. Alternatively, graphical displays can be used to assess the consistency of the treatment effect for varying levels of baseline.

9.2 Adjusting for stratification variables when fitting the LDA model in SAS

An LDA model that adjusts for stratification variables can be fit within SAS using the following code (assuming equal weights for combining estimates across strata):

```
*****************************************************************
**;
** data step necessary prior to running SAS PROC MIXED;
*****************************************************************
**;
DATA long; SET long;
    ARRAY T{4} t0-t3; * time indicator variables;
    ARRAY TT{4} tt0-tt3; * time by treatment 1 (vaccine) indicator variables;
    ** define week times treatment 1 indicator variables;
    DO i = 1 TO 4;
        t{i} = (time=(i-1));
        tt{i} = t{i}*(trt=1);
    END;
    DROP i;
RUN;

*****************************************************************
**;
** LDA model fit in SAS PROC MIXED;
*****************************************************************
**;
PROC MIXED DATA=long;
    CLASS subj time strata;
    MODEL y=strata time strata*time tt1 tt2 tt3/ddfm=KR;
    REPEATED time / SUBJECT=subj TYPE=UN;
    ESTIMATE 'T1 Diff (V-P)' tt1 1;
    ESTIMATE 'T2 Diff (V-P)' tt2 1;
    ESTIMATE 'T3 Diff (V-P)' tt3 1;
    ESTIMATE 'T1 Placebo LSM' time -3 3 0 0
                    strata*time -1 -1 -1 1 1 1 0 0 0 0 0 0 / divisor = 3;
    ESTIMATE 'T2 Placebo LSM' time -3 0 3 0
                    strata*time -1 -1 -1 0 0 0 1 1 1 0 0 0 / divisor = 3;
    ESTIMATE 'T3 Placebo LSM' time -3 0 0 3
                    strata*time -1 -1 -1 0 0 0 0 0 0 1 1 1 / divisor = 3;
    ESTIMATE 'T1 Vaccine LSM' time -3 3 0 0 tt1 3
                    strata*time -1 -1 -1 1 1 1 0 0 0 0 0 0 / divisor = 3;
    ESTIMATE 'T2 Vaccine LSM' time -3 0 3 0 tt2 3
                    strata*time -1 -1 -1 0 0 0 1 1 1 0 0 0 / divisor = 3;
    ESTIMATE 'T3 Vaccine LSM' time -3 0 0 3 tt3 3
                    strata*time -1 -1 -1 0 0 0 0 0 0 1 1 1 / divisor = 3;
    ODS OUTPUT Estimates=outm1;
RUN;
```

Note that this model does not implicitly assume that the baseline means or the correlation between the baseline and post-baseline measurements are the same for each stratum. The typical Longitudinal ANCOVA model that does make this implicit assumption is fit within SAS using the following code:

```
**********************************************************************;
** Longitudinal ANCOVA model fit in SAS PROC MIXED;
**********************************************************************;
PROC SQL NOPRINT;
    SELECT mean(y) INTO: bb
    FROM long WHERE time=0;
QUIT;
PROC MIXED DATA=long;
    WHERE time>0;
    CLASS subj time trt strata;
    MODEL cy = bl trt time trt*time bl*time strata strata*time/ddfm=KR;
    REPEATED time / SUBJECT=subj TYPE=UN;
    LSMEANS trt trt*time / pdiff at bl=&bb;
    ODS OUTPUT LSMeans=outm2a Diffs=outm2b;
RUN;
```

Note that for a stratification factor included in the analysis model the SAS default LSMEANS will apply equal weight over the levels of the stratification factor. In order to use different weights, such as a weight proportional to number of subjects in each level of the stratification factor in the analysis dataset, the OM option may be used in the LSMEANS statement. If the ESTIMATE statement is used, a two-step approach may be considered to incorporate a different weighting scheme for the stratification factor [10].

10. Standard template language for DAS/SAP

Recommended template language on the use of the cLDA model for analyzing longitudinal clinical trials with adjustment for baseline is provided below. This template language is also applicable in the special case where T=1. For completeness, the template is also given for the regular LDA model without adjustment for baseline, which may be used for studies without baseline or when baseline is not informative for the analysis.

For cLDA Model (with adjustment for baseline)

In the primary analysis, a constrained longitudinal data analysis (cLDA) method proposed by Liang and Zeger [4] will be used. This model assumes a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. In this model, the response vector consists of baseline and the values observed at each post-baseline time point. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The analysis model will also adjust for factor1, factor2, … (add other adjustment factors here, if applicable, and consider the time by factor interaction terms, as appropriate). The treatment difference in terms of mean change from baseline to a given time point will be estimated and tested from this model. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The Kenward-Roger adjustment will be used with restricted (or residual) maximum likelihood (REML) to make proper statistical inference.

Although the baseline measurement is included in the response vector, it is independent of treatment, and hence, the baseline means are constrained to be the same for different treatment groups. Of note, in the event that there are no missing data, the estimated treatment difference from the above cLDA model will be identical to that from a traditional longitudinal ANCOVA model which uses the baseline value as a covariate. However, unlike longitudinal ANCOVA, the cLDA model accounts for variability in the baseline values, thus providing more accurate standard errors and confidence intervals for individual treatment effects. Moreover, this model allows the inclusion of patients who are missing either the baseline or post-baseline measurements, thereby increasing efficiency. Details of the model specification, assumptions, and SAS implementation codes are given in Appendix II.

The above REML-based analysis assumes that the vector of model-based residuals follows a multivariate normal distribution. Under severe departures from normality, the REML-based analysis can be inefficient or potentially misleading. Accordingly, the residuals from the REML-based analysis, scaled by the inverse Cholesky root of the marginal variance-covariance matrix, will be subjected to a test for normality. If normality is not rejected at the α=0.001 level, then the above REML-based analysis will serve as the primary analysis. However, if normality is rejected, then the primary analysis will be conducted using multiple imputation (MI) of missing values (if any) in conjunction with a robust regression (RREG) approach that uses M-

estimation. Details of the normality test and the MI→RREG method, along with sample SAS code, are provided in Appendix xx. Of note, the 0.001 level for the normality test was chosen so that the default REML-based analysis is abandoned only under a clear departure from normality; moreover, this choice guarantees that there is no material inflation in the type I error rate for the treatment effect comparison due to a potential correlation between the test statistics for the treatment effect and the normality test.

For LDA Model (without adjustment for baseline)

In the primary analysis, a longitudinal data analysis (LDA) method will be used. This model assumes a different mean for each treatment at each of the repeated time points in the analysis. In this model, time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The analysis model will also adjust for factor1, factor 2… (add other adjustment factors here, if applicable, and also consider the time by factor interaction terms, as appropriate). The treatment difference at a given time point will be estimated and tested from this model. An unstructured covariance matrix will be used to model the correlation among repeated measurements. The Kenward-Roger adjustment will be used with restricted (or residual) maximum likelihood (REML) to make proper statistical inference.

Of note, in the event that there are no missing data, the estimated treatment difference from the above LDA model will be identical to that from a corresponding traditional ANOVA model at a given time point. However, the LDA model allows the inclusion of patients who have missing data at certain time points, thereby increasing efficiency. Details of the model specification, assumptions, and SAS implementation code are given in Appendix 2.

The above REML-based analysis assumes that the vector of model-based residuals follows a multivariate normal distribution. Under severe departures from normality, the REML-based analysis can be inefficient or potentially misleading. Accordingly, the residuals from the REML-based analysis, scaled by the inverse Cholesky root of the marginal variance-covariance matrix, will be subjected to a test for normality. If normality is not rejected at the α=0.001 level, then the above REML-based analysis will serve as the primary analysis. However, if normality is rejected, then the primary analysis will be conducted using multiple imputation (MI) of missing values (if any) in conjunction with a robust regression (RREG) approach that uses M-estimation. Details of the normality test and the MI→RREG method, along with sample SAS code, are provided in Appendix xx. Of note, the 0.001 level for the normality test was chosen so that the default REML-based analysis is abandoned only under a clear departure from normality; moreover, this choice guarantees that there is no material inflation in the type I error rate for the treatment effect comparison due to a potential correlation between the test statistics for the treatment effect and the normality test.

Note: sample SAS codes for the normality test and the MI→RREG method are provided in Section 4 of the ELSTIC document: *Analysis of Continuous but Potentially Non-Normal Longitudinal Data*

Prepared by the ELSTIC Longitudinal Data Analysis Working Group:

PPD

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Appendix I: Simulation Study

An extensive simulation study was undertaken to assess the performance of the Longitudinal ANCOVA and the LDA models under a variety of scenarios. Treatment difference LSMEAN and individual treatment group LSMEAN estimates were compared with respect to bias, coverage, MSE, Type I error and Power.

We simulated data from two treatment groups (placebo and treatment) and four repeated measures per subject (including baseline). Four scenarios were considered: (a) 50 subjects per treatment group, $\sigma^2 = 1$ at each time point; (b) 50 subjects per treatment group, $\sigma^2 = 4$ at each time point; (c) 30 subjects per treatment group, $\sigma^2 = 4$ at each time point; and (d) 80 subjects per treatment group, $\sigma^2 = 4$ at each time point. Data were generated under (i) multivariate normal (Case 0); (ii) a truncated normal distribution at baseline and multivariate normal post-baseline (Case 1); and (iii) a truncated t-distribution with 3 degrees of freedom at baseline and multivariate t distribution with 3 degrees of freedom post-baseline (Case 2). The following correlation structure used was used when generating the data:

$$\begin{bmatrix} 1 & 0.7 & 0.4 & 0.2 \\ 0.7 & 1 & 0.7 & 0.4 \\ 0.4 & 0.7 & 1 & 0.7 \\ 0.2 & 0.4 & 0.7 & 1 \end{bmatrix}$$

For all cases, data were generated with a mean vector for the placebo group of $\mu = (3.0 \;\; 2.5 \;\; 2.3 \;\; 2.0)$. For Cases 1 and 2, the baseline distribution was left-truncated at 2. The post-baseline means under the alternative were chosen to target ~80% power under each scenario when no data were missing. In the analysis, an unstructured covariance matrix was assumed. Two missing data scenarios were considered: (i) no missing data; and (ii) 10% of baseline measurements missing completely at random and a monotone MAR missing data mechanism post-baseline. The probability a post-baseline measurement was missing depended on the measurement at the previous time point, with higher values resulting in a higher probability of drop-out. The percent of data missing by study week is shown in Table 2 for each scenario.

Table 2
Summary of Percent of Data Missing in Simulation Study

	Baseline	Time 1	Time 2	Time 3
CASE 0				
Placebo/Treatment (under null)	~10%	~13%	~22%	~30%
Placebo (under alt)	~10%	~13%	~22%	~30%
Treatment (under alt)	~10%	~19%	~31%	~40%
CASE 1				
Placebo/Treatment (under null)	~10%	~18%	~29%	~37%
Placebo (under alt)	~10%	~18%	~29%	~37%
Treatment (under alt)	~10%	~25%	~40%	~49%
CASE 2				
Placebo/Treatment (under null)	~10%	~22%	~34%	~42%
Placebo (under alt)	~10%	~22%	~34%	~42%
Treatment (under alt)	~10%	~29%	~44%	~53%

Results under the null hypothesis are provided in Tables 3 and 4 for the treatment difference LSMEAN estimate and individual LSMEAN estimates, respectively. Similar results are provided in Tables 5 and 6 under the alternative. The results indicate the following:

- When there are no missing data, the Longitudinal ANCOVA and the LDA models are generally comparable with respect to treatment group comparisons.
- In the presence of missing baseline data, the LDA model has superior power to detect treatment differences.
- In both cases (missing or no missing data), confidence intervals for the least square means (LSMEANS) of the individual treatment groups are not covered at the appropriate 100(1-α)% level in the Longitudinal ANCOVA model.
- Both models were robust to mild departures from normality and quite inefficient under more severe departures from normality. As such, other non-parametric methods may be considered if a considerable departure from normality is suspected.
- In the presence of missing data, the LDA model also resulted in treatment group estimates that did not always cover at the appropriate 100(1-α)% level when the data were not multivariate normal. However, this may be explained by the small effective sample sizes, as the appropriate coverage was attained in the LDA model when no data were missing.

An additional scenario was considered to assess the coverage of the confidence intervals for the LSMEANS of the individual treatment groups with "large" sample sizes in the optimal situation where the data are multivariate normal (Case 0) and no data are missing: (e) 250

subjects per treatment group, $\sigma^2 = 4$ at each time point. Results are provided in Table 7, and clearly demonstrate that the confidence intervals for the LSMEANS of the individual treatment groups are not covered at the appropriate 100(1-α)% level in the Longitudinal ANCOVA model regardless of sample size.

A separate set of simulation studies were conducted to compare the following three methods for computing the denominator degrees of freedom for the tests of fixed effects in the context of small samples: (1) the between-within method (SAS default), DDFM=BETWITHIN (or DDFM=BW); (2) a general Satterthwaite approximation, DDFM=SATTERTH (or DDFM=SAT); and (3) the Kenward-Roger adjustment, DDFM=KENWARDROGER (or DDFM=KR). We simulated data from two treatment groups (placebo and treatment) and three repeated measures per subject (including baseline). Under the null hypothesis H_0, the mean vector was (3.0, 2.5, 2.0) for both groups; under the alternative hypothesis H_1, the mean vector was (3.0, 2.5, 2.0) for the placebo group, and (3.0, 2.0, 1.0) for the treatment group. The variance-covariance matrix for the repeated measures was

$$4\begin{bmatrix} 1 & 0.8 & 0.6 \\ 0.8 & 1 & 0.8 \\ 0.6 & 0.8 & 1 \end{bmatrix}$$

The endpoint was change from baseline at the last time point (t=2). Each simulated data set consisted of 20 subjects with 12 on placebo and 8 on treatment (unbalanced allocation). Twenty thousand (20,000) simulated data sets were generated for each case. Three degrees of missing data were considered under both H_0 and H_1: (1) no missing data; (2) low amount of missing data (~8% at t=1, ~13% at t=2); and (3) moderate amount of missing data (~15% at t=1, ~23% at t=2). The three DDFM methods have no impact on the point estimate of fixed effects, hence the comparison was based on the variance estimates, type I error/power and coverage of 95% CIs. Results are provided in Table 8 for the between-group LSMEAN difference at time 2 and in Table 9 for the LSMEAN change from baseline at time 2 for the treatment group, respectively. The results indicate the following:

- The default variance estimate (as used by DDFM=BW and DDFM=SAT) underestimated the true variability of the fixed effects estimate.
- Although the variance estimates were identical for the DDFM=SAT and DDFM=BW options, the former produced smaller denominator degrees of freedom and resulted in better coverage and less inflated Type I error.
- The DDFM=KR option appropriately adjusted the estimated variance and the denominator degrees of freedom, and produced proper coverage and controlled the Type I error.

Table 3
Simulation Results Comparing the LDA and Longitudinal ANCOVA Models under H_0
LSMEAN Treatment Difference in Change from Baseline at Time 3

Simulation Scenario	Case	LSMEAN OF TREATMENT DIFFERENCE IN CHANGE FROM BASELINE AT TIME 3							
		Bias		Coverage (%)		MSE		Type I Error (%)	
		LDA	Longitudinal ANCOVA	LDA	Longitudinal ANCOVA	LDA	Longitudinal ANCOVA	LDA	Longitudinal ANCOVA
No Missing Data under H_0 (5000 simulations)									
(a)	Case 0	0.000	0.000	95.2	95.4	0.038	0.038	2.3	2.2
n = 50/group,	Case 1	-0.000	-0.000	94.8	95.2	0.038	0.038	2.4	2.3
$\sigma^2 = 1$	Case 2	-0.001	-0.001	95.2	95.6	0.087	0.087	2.6	2.4
(b)	Case 0	-0.002	-0.002	94.9	95.3	0.156	0.156	2.6	2.5
n = 50/group,	Case 1	-0.000	-0.000	95.4	95.5	0.150	0.150	2.3	2.2
$\sigma^2 = 4$	Case 2	-0.001	-0.001	95.2	95.4	0.373	0.373	2.3	2.2
(c)	Case 0	0.002	0.002	94.6	95.0	0.262	0.262	3.0	2.8
n = 30/group,	Case 1	-0.000	-0.000	94.5	94.9	0.261	0.261	2.7	2.5
$\sigma^2 = 4$	Case 2	0.001	0.001	94.8	95.2	0.625	0.625	2.6	2.3
(d)	Case 0	-0.000	-0.000	94.9	95.1	0.095	0.095	2.6	2.5
n = 80/group,	Case 1	0.000	0.000	95.1	95.2	0.096	0.096	2.7	2.5
$\sigma^2 = 4$	Case 2	0.002	0.002	95.2	95.3	0.228	0.228	2.3	2.3
Missing Data under H_0 (5000 simulations)									
(a)	Case 0	0.002	0.002	95.0	95.4	0.048	0.048	2.4	2.3
n = 50/group,	Case 1	-0.001	-0.001	95.5	95.8	0.050	0.050	2.2	2.0
$\sigma^2 = 1$	Case 2	-0.003	-0.003	94.6	95.1	0.098	0.098	2.7	2.5
(b)	Case 0	-0.003	-0.003	94.8	95.1	0.213	0.213	2.6	2.6
n = 50/group,	Case 1	-0.003	-0.003	95.1	95.3	0.225	0.225	2.5	2.3
$\sigma^2 = 4$	Case 2	0.003	0.002	95.1	95.4	0.428	0.428	2.3	2.2
(c)	Case 0	-0.000	-0.000	94.6	95.1	0.358	0.358	2.9	2.7
n = 30/group,	Case 1	0.002	0.002	94.5	95.2	0.397	0.397	2.6	2.3
$\sigma^2 = 4$	Case 2	-0.013	-0.013	94.0	94.6	0.744	0.744	3.0	2.7
(d)	Case 0	0.002	0.002	94.9	95.1	0.130	0.130	2.9	2.8
n = 80/group,	Case 1	0.000	0.000	94.4	94.5	0.145	0.145	2.8	2.7
$\sigma^2 = 4$	Case 2	-0.002	-0.002	94.4	94.6	0.257	0.257	3.0	3.0

Table 4
Simulation Results Comparing the LDA and Longitudinal ANCOVA Models under H_0
LSMEAN of Change from Baseline at Time 3 for Placebo and Treatment Groups

Simulation Scenario	Case	LSMEAN of change from baseline at Time 3 for Placebo				LSMEAN of change from baseline at Time 3 for Treatment			
		% Bias		Coverage (%)		% Bias		Coverage	
		LDA	Longitudinal ANCOVA	LDA	Longitudinal ANCOVA	LDA	Longitudinal ANCOVA	LDA	Longitudinal ANCOVA
No Missing Data under H_0 (5000 simulations)									
(a)	Case 0	0.01%	0.01%	95.2	91.5	-0.01%	-0.01%	95.2	91.1
n = 50/group,	Case 1	-0.02%	-0.02%	94.6	92.2	0.02%	0.02%	95.3	93.1
$\sigma^2 = 1$	Case 2	-0.03%	-0.03%	95.4	92.8	0.03%	0.03%	94.4	91.1
(b)	Case 0	-0.10%	-0.10%	95.3	91.5	0.10%	0.10%	95.4	91.4
n = 50/group,	Case 1	0.00%	0.00%	95.5	93.7	0.00%	0.00%	95.5	94.1
$\sigma^2 = 4$	Case 2	-0.03%	-0.03%	94.5	91.2	0.03%	0.03%	95.1	92.1
(c)	Case 0	0.08%	0.08%	95.0	90.9	-0.08%	-0.08%	94.9	90.9
n = 30/group,	Case 1	-0.01%	-0.01%	94.7	92.9	0.01%	0.01%	94.5	93.1
$\sigma^2 = 4$	Case 2	0.03%	0.03%	94.8	91.8	-0.03%	-0.03%	94.8	91.9
(d)	Case 0	0.00%	0.00%	94.9	91.2	0.00%	0.00%	95.2	91.2
n = 80/group,	Case 1	0.01%	0.01%	95.1	93.3	-0.01%	-0.01%	94.6	92.8
$\sigma^2 = 4$	Case 2	0.05%	0.05%	95.4	92.4	-0.05%	-0.05%	94.9	92.3
Missing Data under H_0 (5000 simulations)									
(a)	Case 0	0.04%	0.04%	95.1	92.3	-0.11%	-0.11%	95.1	92.0
n = 50/group,	Case 1	0.09%	0.09%	94.9	92.8	0.18%	0.18%	95.2	93.7
$\sigma^2 = 1$	Case 2	-0.20%	-0.20%	94.4	91.6	0.00%	0.00%	93.6	90.7
(b)	Case 0	-0.54%	-0.54%	94.6	92.0	-0.29%	-0.29%	94.6	92.1
n = 50/group,	Case 1	-0.22%	-0.22%	94.4	93.7	-0.04%	-0.04%	94.7	94.2
$\sigma^2 = 4$	Case 2	0.14%	0.18%	91.9	91.1	0.02%	0.06%	91.5	91.0
(c)	Case 0	-0.05%	-0.05%	94.6	92.4	-0.04%	-0.04%	94.2	91.9
n = 30/group,	Case 1	0.03%	0.03%	93.5	93.2	-0.10%	-0.10%	94.5	94.0
$\sigma^2 = 4$	Case 2	-0.82%	-0.82%	91.3	91.2	-0.22%	-0.22%	92.0	91.6

Simulation Scenario	Case	LSMEAN of change from baseline at Time 3 for Placebo				LSMEAN of change from baseline at Time 3 for Treatment			
		% Bias		Coverage (%)		% Bias		Coverage	
		LDA	Longitudinal ANCOVA	LDA	Longitudinal ANCOVA	LDA	Longitudinal ANCOVA	LDA	Longitudinal ANCOVA
(d)	Case 0	0.10%	0.10%	94.7	91.9	-0.08%	-0.09%	94.9	92.5
n = 80/group,	Case 1	0.02%	0.02%	94.6	94.0	0.01%	0.01%	94.0	93.3
$\sigma^2 = 4$	Case 2	-0.18%	-0.17%	91.2	90.4	-0.07%	-0.06%	90.9	90.1

Table 5
Simulation Results Comparing the LDA and Longitudinal ANCOVA Models under H_1
LSMEAN Treatment Difference in Change from Baseline at Time 3

Simulation Scenario	Case	LSMEAN OF TREATMENT DIFFERENCE IN CHANGE FROM BASELINE AT TIME 3							
		% Bias		Coverage (%)		MSE		Power	
		LDA	Longitudinal ANCOVA	LDA	Longitudinal ANCOVA	LDA	Longitudinal ANCOVA	LDA	Longitudinal ANCOVA
No Missing Data under H_1 (2000 simulations)									
(a)	Case 0	-0.19%	-0.19%	94.3	94.5	0.040	0.040	85.8	85.4
n = 50/group,	Case 1	0.11%	0.11%	94.6	95.0	0.039	0.039	86.0	85.5
$\sigma^2 = 1$	Case 2	-0.18%	-0.18%	94.3	94.5	0.093	0.093	55.1	54.4
(b)	Case 0	0.13%	0.13%	94.7	94.9	0.156	0.156	83.9	83.2
n = 50/group,	Case 1	0.15%	0.15%	95.1	95.3	0.158	0.158	82.8	82.1
$\sigma^2 = 4$	Case 2	-0.17%	-0.17%	95.1	95.3	0.377	0.377	48.3	47.5
(c)	Case 0	0.19%	0.19%	94.7	95.3	0.265	0.265	82.2	81.3
n = 30/group,	Case 1	-0.25%	-0.25%	94.2	95.0	0.268	0.268	82.7	81.8
$\sigma^2 = 4$	Case 2	0.23%	0.23%	94.8	95.3	0.598	0.598	51.9	50.4
(d)	Case 0	-0.19%	-0.19%	94.8	94.9	0.098	0.098	82.2	81.9
n = 80/group,	Case 1	-0.13%	-0.13%	95.1	95.3	0.095	0.095	83.0	82.3
$\sigma^2 = 4$	Case 2	0.14%	0.14%	96.2	96.2	0.229	0.229	49.1	48.6
Missing Data under H_1 (2000 simulations)									
(a)	Case 0	-0.63%	-0.62%	94.5	94.8	0.054	0.054	75.1	73.9
n = 50/group,	Case 1	0.35%	0.40%	94.7	95.2	0.053	0.053	74.7	73.7
$\sigma^2 = 1$	Case 2	-0.72%	-0.71%	94.7	95.1	0.105	0.105	49.6	48.6
(b)	Case 0	-0.38%	-0.38%	94.0	94.3	0.237	0.237	69.3	67.8
n = 50/group,	Case 1	0.38%	0.38%	95.0	95.2	0.258	0.258	62.0	61.0
$\sigma^2 = 4$	Case 2	-0.47%	-0.47%	95.0	95.3	0.464	0.464	40.5	39.4
(c)	Case 0	1.11%	1.11%	94.3	94.8	0.382	0.382	68.9	67.3
n = 30/group,	Case 1	-0.98%	-0.98%	93.6	94.3	0.455	0.455	61.7	60.1
$\sigma^2 = 4$	Case 2	2.01%	2.01%	94.1	95.2	0.733	0.733	42.9	40.8

Simulation Scenario	Case	LSMEAN OF TREATMENT DIFFERENCE IN CHANGE FROM BASELINE AT TIME 3							
		% Bias		Coverage (%)		MSE		Power	
		LDA	Longitudinal ANCOVA	LDA	Longitudinal ANCOVA	LDA	Longitudinal ANCOVA	LDA	Longitudinal ANCOVA
(d)	Case 0	-0.87%	-0.87%	95.3	95.7	0.139	0.139	67.9	67.5
n = 80/group,	Case 1	-0.83%	-0.83%	94.2	94.4	0.165	0.165	62.2	61.0
$\sigma^2 = 4$	Case 2	1.01%	1.01%	95.0	95.5	0.277	0.277	42.6	41.4

Table 6
Simulation Results Comparing the LDA and Longitudinal ANCOVA Models under H_1
LSMEAN of Change from Baseline at Time 3 for Placebo and Treatment Groups

Simulation Scenario	Case	LSMEAN of change from baseline at Time 3 for Placebo				LSMEAN of change from baseline at Time 3 for Treatment			
		% Bias		Coverage (%)		% Bias		Coverage	
		LDA	Longitudinal ANCOVA	LDA	Longitudinal ANCOVA	LDA	Longitudinal ANCOVA	LDA	Longitudinal ANCOVA
No Missing Data under H_1 (2000 simulations)									
(a)	Case 0	0.06%	0.06%	95.2	91.6	-0.04%	-0.04%	94.9	91.6
n = 50/group,	Case 1	-0.03%	-0.03%	94.9	92.1	0.02%	0.02%	95.2	92.6
$\sigma^2 = 1$	Case 2	0.04%	0.04%	93.9	90.4	-0.03%	-0.03%	94.5	91.9
(b)	Case 0	-0.08%	-0.08%	95.2	91.8	0.04%	0.04%	94.6	90.5
n = 50/group,	Case 1	-0.05%	-0.05%	94.7	92.9	0.03%	0.03%	95.6	93.4
$\sigma^2 = 4$	Case 2	0.04%	0.04%	94.6	91.3	-0.03%	-0.03%	94.6	91.3
(c)	Case 0	-0.14%	-0.14%	94.6	90.0	0.06%	0.06%	95.4	92.1
n = 30/group,	Case 1	0.10%	0.10%	95.4	93.6	-0.06%	-0.06%	94.2	92.4
$\sigma^2 = 4$	Case 2	-0.08%	-0.08%	95.3	92.2	0.05%	0.05%	95.1	92.3
(d)	Case 0	0.09%	0.09%	94.6	91.3	-0.05%	-0.05%	95.7	91.5
n = 80/group,	Case 1	0.03%	0.03%	95.5	93.9	-0.02%	-0.02%	94.6	92.8
$\sigma^2 = 4$	Case 2	-0.03%	-0.03%	94.8	92.3	0.02%	0.02%	95.3	91.9

Simulation Scenario	Case	LSMEAN of change from baseline at Time 3 for Placebo				LSMEAN of change from baseline at Time 3 for Treatment			
		% Bias		Coverage (%)		% Bias		Coverage	
		LDA	Longitudinal ANCOVA	LDA	Longitudinal ANCOVA	LDA	Longitudinal ANCOVA	LDA	Longitudinal ANCOVA
Missing Data under H_1 (2000 simulations)									
(a)	Case 0	0.37%	0.37%	94.6	92.1	-0.01%	-0.01%	95.1	92.0
n = 50/group,	Case 1	-0.11%	-0.11%	94.8	93.0	0.04%	0.04%	94.7	93.4
$\sigma^2 = 1$	Case 2	0.15%	0.29%	93.2	90.3	-0.11%	-0.01%	94.6	91.9
(b)	Case 0	0.03%	0.02%	93.6	92.2	-0.19%	-0.19%	93.9	91.8
n = 50/group,	Case 1	-0.20%	-0.20%	93.7	93.4	0.03%	0.02%	94.7	93.9
$\sigma^2 = 4$	Case 2	0.69%	0.69%	91.2	90.9	0.30%	0.30%	90.4	89.4
(c)	Case 0	-1.82%	-1.82%	93.4	91.6	-0.08%	-0.08%	94.4	92.5
n = 30/group,	Case 1	0.65%	0.65%	94.2	94.4	-0.09%	-0.09%	93.6	93.2
$\sigma^2 = 4$	Case 2	-0.52%	-0.52%	90.3	90.4	0.48%	0.48%	91.4	90.8
(d)	Case 0	0.54%	0.54%	94.7	92.8	-0.13%	-0.13%	95.2	93.0
n = 80/group,	Case 1	0.08%	0.08%	94.4	94.1	-0.22%	-0.22%	94.0	93.2
$\sigma^2 = 4$	Case 2	-0.15%	-0.15%	91.0	91.3	0.19%	0.19%	91.2	89.9

Table 7
Simulation Results Comparing the LDA and Longitudinal ANCOVA Models under H_1
LSMEAN of Change from Baseline at Time 3 for Placebo and Treatment Groups

Simulation Scenario	Case	LSMEAN of change from baseline at Time 3 for Placebo				LSMEAN of change from baseline at Time 3 for Treatment			
		% Bias		Coverage (%)		% Bias		Coverage	
		LDA	Longitudinal ANCOVA	LDA	Longitudinal ANCOVA	LDA	Longitudinal ANCOVA	LDA	Longitudinal ANCOVA
No Missing Data under H_1 (2000 simulations)									
(c) n = 30/group, $\sigma^2 = 4$	Case 0	-0.14%	-0.14%	94.6	90.0	0.06%	0.06%	95.4	92.1
(b) n = 50/group, $\sigma^2 = 4$	Case 0	-0.08%	-0.08%	95.2	91.8	0.04%	0.04%	94.6	90.5
(d) n = 80/group, $\sigma^2 = 4$	Case 0	0.09%	0.09%	94.6	91.3	-0.05%	-0.05%	95.7	91.5
(d) n = 250/group, $\sigma^2 = 4$	Case 0	0.03%	0.03%	94.3	90.2	0.02%	0.02%	95.5	91.6

Table 8
Simulation Results Comparing Three DDFM Methods
LSMEAN Treatment Difference in Change from Baseline at Time 2

		Avg. of Estimated Variance			Type I Error/Power (%)			Empirical Coverage (%)		
Simulation Scenario	**Monte Carlo Variance**	**BW**	**SAT**	**KR**	**BW**	**SAT**	**KR**	**BW**	**SAT**	**KR**
Under H_0 (20,000 simulations)										
No missing	0.567	0.504	0.504	0.560	6.4	6.3	5.2	93.6	93.7	94.8
Low missing	0.660	0.568	0.568	0.656	7.1	6.7	5.1	92.9	93.3	94.9
Moderate missing	0.758	0.639	0.639	0.777	7.5	6.7	4.8	92.5	93.3	95.2
Under H_1 (20,000 simulations)										
No missing	0.567	0.504	0.504	0.560	27.9	27.7	24.6	93.6	93.7	94.8
Low missing	0.656	0.565	0.565	0.651	26.5	25.7	22.0	93.0	93.4	95.0
Moderate missing	0.749	0.632	0.632	0.765	25.2	23.8	19.3	92.6	93.3	95.3

Table 9
Simulation Results Comparing Three DDFM Methods
LSMEAN Change from Baseline at Time 2 for the Treatment Group

		Avg. of Estimated Variance			Empirical Coverage (%)		
Simulation Scenario	**Monte Carlo Variance**	**BW**	**SAT**	**KR**	**BW**	**SAT**	**KR**
Under H_1 (20,000 simulations)							
No missing	0.368	0.342	0.342	0.362	94.2	94.1	94.7
Low missing	0.422	0.380	0.380	0.414	93.7	93.8	94.8
Moderate missing	0.493	0.423	0.423	0.479	93.1	93.4	94.8

Appendix II: Sample Protocol Appendix for Model Details and SAS Implementation

Appendix for cLDA Model (with adjustment for baseline)

Let Y_{ijt} be the response for subject *i,* with treatment assignment *j*, at time *t*. The marginal mean responses of the cLDA model can be formulated as

$$E(Y_{ij0}) = \gamma_0, \quad t = 0,$$

and

$$E(Y_{ijt}) = \gamma_0 + \gamma_{jt}, \quad j = 0,1, \quad t = 1,2,...,T.$$

The mean response γ_0 at t =0 is constrained to be the same for both treatment groups due to randomization. The effect γ_{jt} denotes the change from baseline for treatment *j* at time *t*. The cLDA model assumes that baseline and post-baseline values have a joint multivariate normal distribution. An unstructured covariance matrix can be specified in the mixed model to account for within subject correlation at times $t \geq 0$ (including baseline).

The treatment difference for the mean change from baseline at time point *t*, $t = 1,2,..., T$ is defined as:

$$\eta_t = \gamma_{1t} - \gamma_{0t}.$$

At each time point *t*, $t = 1,2,..., T$, the mean change from baseline (LSMEANS) for test drug and control are γ_{1t} and γ_{0t}, respectively, as defined in the cLDA model above.

This longitudinal model provides valid statistical inference in the presence of possible missing data if the missing data mechanism is ignorable (or more specifically, missing at random [MAR] or missing completely at random [MCAR]). This missing data mechanism requires that the probability of a data point being missing does not depend on the missing data after adjusting for the observed data. *Some justification may be provided here, for example:*

In this study, we expect that MAR/MCAR mechanisms will underlie most of the missingness and the proportion of data missing not at random [MNAR], driven solely by unobserved values of the study endpoints, will be small. Specifically, discontinuation reasons may include lack of efficacy, clinical or laboratory AEs, relocation, withdrawal of consent, protocol violations, and/or data processing issues. Reasons such as relocation and data processing issues are likely to be MCAR. On the other hand, lack of efficacy may belong to MAR because the discontinuation may depend on the observed efficacy outcomes. The MAR or MNAR mechanisms might each underlie the other reasons to some extent. If treatment in large part determines the loss of data for these other reasons (such as clinical or laboratory

AEs), the mechanism may be close to MAR because treatment assignment is an observed variable and included in the analysis model. Based on prior study results, missing data due to other reasons is relatively infrequent.

Sample SAS code is provided below to fit the full likelihood cLDA model. *(project teams are responsible to modify the following code according to their requirements)*

For example, assume that there is a baseline and three post-baseline measurements from a vaccine trial. The primary interest here is to compare the treatments (vaccine vs. placebo) in terms of mean change from baseline in longitudinal clinical trial. The full likelihood LDA method models the response as a function of treatment, time and the interaction of time by treatment.

```
*****************************************************************;
** data step necessary prior to running SAS PROC MIXED;
*****************************************************************;
DATA long; SET long;
ARRAY T{4} t0-t3; * time indicator variables;
ARRAY TT{4} tt0-tt3; * time by treatment 1 (vaccine) indicator variables;
** define week times treatment 1 indicator variables;
DO i = 1 TO 4;
t{i} = (time=(i-1));
tt{i} = t{i}*(trt=1);
END;
DROP i;
RUN;
*****************************************************************;
** LDA model fit in SAS PROC MIXED;
*****************************************************************;
PROC MIXED DATA=long;
CLASS subj time;  ** subj is the patient id number **;
MODEL y=time tt1 tt2 tt3/ddfm=KR;
REPEATED time / SUBJECT=subj TYPE=UN;
ESTIMATE 'T1 Diff (V-P)' tt1 1;
ESTIMATE 'T2 Diff (V-P)' tt2 1;
ESTIMATE 'T3 Diff (V-P)' tt3 1;
ESTIMATE 'T1 Placebo LSM' time -1 1 0 0;
ESTIMATE 'T2 Placebo LSM' time -1 0 1 0;
ESTIMATE 'T3 Placebo LSM' time -1 0 0 1;
ESTIMATE 'T1 Vaccine LSM' time -1 1 0 0 tt1 1;
ESTIMATE 'T2 Vaccine LSM' time -1 0 1 0 tt2 1;
ESTIMATE 'T3 Vaccine LSM' time -1 0 0 1 tt3 1;
ODS OUTPUT Estimates=outm1;
RUN;
```

Appendix for LDA Model (without adjustment for baseline)

Let Y_{ijt} be the response for subject *i,* with treatment assignment *j*, at time *t*. The marginal mean responses of the full likelihood LDA model is modeled as

$$E(Y_{ijt}) = \gamma_{jt}, \quad j = 0,1, \quad t = 1,2,.....,T,$$

The LDA model assumes that repeated measurements follow a multivariate normal distribution. An unstructured covariance matrix can be specified in the mixed model to account for within subject correlation.

The treatment difference at time point *t*, $t = 1,2,..., T$ is defined as:

$$\eta_t = \gamma_{1t} - \gamma_{0t}.$$

For $t = 1,2,..., T$, the mean response (LSMEANS) for test drug and control are γ_{1t} and γ_{0t}, respectively, as defined in the LDA model above.

This longitudinal model provides valid statistical inference in the presence of possible missing data if the missing data mechanism is ignorable (or more specifically, missing at random [MAR] or missing completely at random [MCAR]). This missing data mechanism requires that the probability of a data point being missing does not depend the missing data after adjusting for the observed data. *Some justification may be provided here, for example:*

In this study, we expect that MAR/MCAR mechanisms will underlie most of the missingness and the proportion of data missing not at random [MNAR], driven solely by unobserved values of the study endpoints, will be small. Specifically, the discontinuation reasons may include lack of efficacy, clinical or laboratory AEs, relocation, withdrawal of consent, protocol violations, and/or data processing issues. Reasons such as relocation and data processing issues, are likely to be MCAR. On the other hand, lack of efficacy may belong to MAR because the discontinuation may depend on the observed efficacy outcomes. The MAR or MNAR mechanisms might each underlie the other reasons to some extent. If treatment in large part determines the loss of data for these other reasons (such as clinical or laboratory AEes), the mechanism may be close to MAR since treatment assignment is an observed variable and included in the analysis model. Based on the prior study results, missing data due to other reasons is relatively infrequent.

Sample SAS code is provided below to fit the full likelihood LDA model. *(project teams are responsible to modify the following code according to their requirements)*

For example, assume that there are three repeated measurements from a vaccine trial. The primary interest here is to compare the treatments (vaccine vs. placebo) at last time point in this longitudinal clinical trial. The full likelihood LDA method models the response as a function of treatment, time and the interaction of time by treatment.

```
**********************************************************************;
** LDA model fit in SAS PROC MIXED;
**********************************************************************;
PROC MIXED DATA=long;
CLASS subj trt time;  ** subj is the patient id number, trt is the treatment variable, time is the time points for repeated measures **;
MODEL y=trt time trt*time / noint ddfm=KR;
REPEATED time / SUBJECT=subj TYPE=UN;
ESTIMATE 'T1 Diff (V-P)' trt -1 1 trt*time -1 0 0  1 0 0 ;
ESTIMATE 'T2 Diff (V-P)' trt -1 1 trt*time  0 -1 0  0 1 0 ;
ESTIMATE 'T3 Diff (V-P)' trt -1 1 trt*time  0 0 -1  0 0 1 ;
ESTIMATE 'T1 Placebo LSM' trt 1 0 time 1 0 0 trt*time 1 0 0  0 0 0;
ESTIMATE 'T2 Placebo LSM' trt 1 0 time 0 1 0 trt*time 0 1 0  0 0 0;
ESTIMATE 'T3 Placebo LSM' trt 1 0 time 0 0 1 trt*time 0 0 1  0 0 0;
ESTIMATE 'T1 Vaccine LSM' trt 0 1 time 1 0 0 trt*time 0 0 0  1 0 0;
ESTIMATE 'T2 Vaccine LSM' trt 0 1 time 0 1 0 trt*time 0 0 0  0 1 0;
ESTIMATE 'T3 Vaccine LSM' trt 0 1 time 0 0 1 trt*time 0 0 0  0 0 1;
ODS OUTPUT Estimates=outm1;
RUN;
```

Appendix 5 Predefined Limits of Change Criteria

Table 1
Predefined Limits of Change Criteria for Laboratory Data

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

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

Table 2
Predefined Limits of Change Criteria for Vital Signs, Weight, and Temperature

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

Table 3
Predefined Limits of Change Criteria for ECGs

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

INVESTIGATOR SIGNATURE PAGE

Abbreviated Title	A Long Term Safety Trial of MK-8931 in AD (EPOCH)
Title	A Parallel-Group, Double Blind Long Term Safety Trial of MK-8931 in Subjects with Alzheimer's Disease. (Phase 2/3; Protocol No. MK-8931-017-21) (also known as SCH 900931, P07738)
Sponsor	One Merck Drive P.O. Box 100 Whitehouse Station, NJ 08889-0100, U.S.A.
Trial Physician/Director	PPD
Date of Finalization of This Current Version of the Protocol	**01-AUG-2016** – Amendment 017-21(France Specific)
Previous Versions of the Protocol	**26-JUL-2016**– Amendment No.20 (Country Specific) **22-JUL-2016**– Amendment No.19 (France Specific) **21-JUL-2016**– Amendment No.18 (Country Specific) **28-JUN-2016** – Amendment No.17 **11-Sep-2015 –** Amendment 017-16 (France Specific) **26 JUN 2015** – Amendment 017-15 France Specific **24 APR 2015 -** Amendment 017-14 Country Specific **09 APR 2015 -** Amendment 017-13 **05 MAR 2015** – Amendment 017-12 Country Specific **26 FEB 2015 –** Amendment 017-11 Country Specific **18-DEC-2014**– Amendment 017-10 **08 AUG 2014** - Amendment 017-09 Country Specific **11 FEB 2014** – Amendment #5 (017-08) **14 AUG 2013** – Amendment #4 (017-07) **08 NOV 2012** – Amendment #3 Brazil Version 1 (017-06) **26 SEP 2012** – Amendment #3 (017-05) **23 JUL 2012** – Amendment #2 Brazil Version 2 (017-04) **23 JUL 2012** – Amendment #2 Brazil Version 1 (017-03) **20 JUN 2012** - Amendment #2 (017-02) **31 MAY 2012** - Amendment #1 (017-01) **19 JAN 2012** - Initial Protocol (017-00)

Name and Degree of Sponsor Representative
Department of Sponsor Representative

dd MMM yyyy

I have read Protocol No. MK-8931-017-21 (also known as P07738) dated **01 AUG 2016**, including all appendices, and agree to conduct the trial in accordance with the protocol. The protocol and trial documents must also be approved by the IRBs/IECs and regulatory authorities as appropriate, before implementation at the site. I agree to implement the protocol and trial documents only after all necessary approvals have been obtained and the sponsor has confirmed that it is acceptable to do so.

Name, Degree, full mailing address of Investigator

Site Number

dd MMM yyyy