Official Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Pharmacokinetics of MK-1942 Administered to Alzheimer's Disease Patients Receiving Donepezil Treatment
NCT number:	NCT04308304
Document Date:	16-Mar-2020

Title Page

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Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Pharmacokinetics of MK-1942 Administered to Alzheimer's Disease Patients Receiving Donepezil Treatment.

Protocol Number: 005-01

Compound Number: MK-1942

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

One Merck Drive

P.O. Box 100

Whitehouse Station, New Jersey, 08889-0100, U.S.A.

Regulatory Agency Identifying Number(s):

IND	139557

Approval Date: 16 March 2020

Sponsor Signatory

Typed Name:
Title:

Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name:
Title:

Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 01	16-MAR-2020	Correction of NIMP designation of donepezil was required to ensure proper safety reporting to regulatory agency. Other editorial changes were implemented and information on the ongoing P004 was updated.
Original Protocol	10-JAN-2020	Not Applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: MK-1942-005-01

Overall Rationale for the Amendments:

Correction of NIMP designation of donepezil was required to ensure proper safety reporting to regulatory agency. Other editorial changes were implemented and information on the ongoing P004 was updated.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Remove 24hr timepoint from footnote "m"	24hr timepoint overlapped with the pre-dose measurement on the following day. Removing this timepoint eliminated the redundant timepoint.
Section 2.2.3.2 MK-1942-004	Added dosing and safety data up to Panel B in P004.	Ensure protocol has the most recent information on the safety and tolerability of MK-1942 in study P004 as of the time of this amendment.
Section 5.2 Exclusion Criteria	Exclusion #10 – removed text below "Is unable to refrain from or anticipates the use of any medication, including prescription and non-prescription drugs or herbal remedies (see Section 6.5, item 8 for specific examples), beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of study drug, throughout the study (including intervals between treatment periods), until the post-study visit. There may be certain medications that are permitted (see Section 6.5)."	PN005 is being conducted in an elderly population likely to be taking prescription medications for chronic conditions. The highlighted section causes confusion around those medications that are permitted in the study. In order to ensure clarity around which concomitant medications are permitted in candidates for enrollment and under what conditions, this section was removed. The remaining text in Exclusion criteria 10 states "All medications being taken by candidates for enrollment in the study should be reviewed by the PI and the Sponsor to determine their propensity for altering MK-1942 exposure, or for MK-1942 to interfere with the metabolism of the medication. Medications prescribed for the candidate that are stably treating a condition should not be interrupted.

Section # and Name	Description of Change	Brief Rationale
Section 6.1 Study Interventions Administered, Table 7	Changed donepezil designation from Investigational Medicinal Product (IMP) to Non-Investigational Medicinal Product (NIMP).	Donepezil was incorrectly labeled as IMP. Correction was needed to ensure proper safety reporting.
Section 6.5 Concomitant Therapy	Removed felbamate, topiramate, probenecid, lamotrigine and riluzole from the list of prohibited concomitant medications	New pre-clinical data suggest that the potential for a DDIs with these drugs is low.
Section 8.10.5 Critical Procedures Based on Study Objectives: Timing of Procedure	Predose safety standard safety evaluations: Added that windows are *prior* to dosing. Changed ECG window from 3hrs to 1 hr prior to dosing.	Editorial change to ensure clarity of interpretation. ECG window narrowed to ensure it is as close to dosing as possible.
Sections 4.2.1.3 Future Biomedical Research, 8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research and Appendix 10.6 Collection and Management of Specimens for Future Biomedical Research	Removal of the word “substudy”	New template requirement

Table of Contents

DOCUMENT HISTORY **3**
PROTOCOL AMENDMENT SUMMARY OF CHANGES **4**
1 PROTOCOL SUMMARY **13**
1.1 Synopsis **13**
1.2 Schema **16**
1.3 Schedule of Activities **18**
2 INTRODUCTION **22**
2.1 Study Rationale **22**
2.2 Background **23**
2.2.1 Pharmaceutical and Therapeutic Background 23
2.2.2 Preclinical and Clinical Studies 23
2.2.3 Ongoing Clinical Studies 23
2.2.3.1 MK-1942-002: A Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study of the Safety, Tolerability and Pharmacokinetics of MK-1942 in Healthy Participants 23
2.2.3.2 MK-1942-004: A Randomized, Double Blind, Placebo-Controlled Investigation of the Safety, Tolerability and Pharmacokinetics of Multiple-Dose Regimens of MK-1942 in Healthy Elderly Participants 37
2.2.4 Information on Other Study-related Therapy 38
2.3 Benefit/Risk Assessment **39**
3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS **39**
4 STUDY DESIGN **40**
4.1 Overall Design **40**
4.2 Scientific Rationale for Study Design **41**
4.2.1 Rationale for Endpoints 42
4.2.1.1 Safety Endpoints 42
Pharmacokinetic Endpoints 43
4.2.1.2 Planned Exploratory Biomarker Research 44
4.2.1.2.1 Planned Genetic Analysis 44
4.2.1.3 Future Biomedical Research 44
4.2.2 Rationale for the Use of Comparator/Placebo 45
4.2.3 Rationale for Suicidal Ideation and Behavior Monitoring 45
4.3 Justification for Dose **45**
4.3.1 Starting Dose for This Study 45
4.3.2 Maximum Dose/Exposure for This Study 46

4.3.3 Rationale for Dose Interval and Study Design 47
4.4 Beginning and End of Study Definition 48
4.4.1 Clinical Criteria for Early Study Termination 48
5 STUDY POPULATION 49
5.1 Inclusion Criteria 49
5.2 Exclusion Criteria 51
5.3 Lifestyle Considerations 54
5.3.1 Meals and Dietary Restrictions 54
5.3.1.1 Diet Restrictions 54
5.3.1.2 Fruit Juice Restrictions 54
5.3.2 Caffeine, Alcohol, and Tobacco Restrictions 54
5.3.2.1 Caffeine Restrictions 54
5.3.2.2 Alcohol Restrictions 55
5.3.2.3 Tobacco Restrictions 55
5.3.3 Activity Restrictions 55
5.4 Screen Failures 55
5.5 Participant Replacement Strategy 55
6 STUDY INTERVENTION 56
6.1 Study Intervention(s) Administered 56
6.2 Preparation/Handling/Storage/Accountability 58
6.2.1 Dose Preparation 58
6.2.2 Handling, Storage, and Accountability 58
6.3 Measures to Minimize Bias: Randomization and Blinding 59
6.3.1 Intervention Assignment 59
6.3.2 Stratification 59
6.3.3 Blinding 59
6.4 Study Intervention Compliance 59
6.5 Concomitant Therapy 59
6.5.1 Rescue Medications and Supportive Care 61
6.6 Dose Modification (Escalation/Titration/Other) 61
6.6.1 Stopping Rules 61
6.6.2 Dizziness/Nausea Stopping Criteria 61
6.7 Intervention After the End of the Study 63
6.8 Clinical Supplies Disclosure 63
7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL 63
7.1 Discontinuation of Study Intervention 63
7.2 Participant Withdrawal From the Study 64

7.3 Lost to Follow-up 65
8 STUDY ASSESSMENTS AND PROCEDURES 65
8.1 Administrative and General Procedures 66
8.1.1 Informed Consent 66
8.1.1.1 General Informed Consent 66
8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research 67
8.1.2 Inclusion/Exclusion Criteria 67
8.1.3 Participant Identification Card 67
8.1.4 Medical History 68
8.1.5 Prior and Concomitant Medications Review 68
8.1.5.1 Prior Medications 68
8.1.5.2 Concomitant Medications 68
8.1.6 Assignment of Screening Number 68
8.1.7 Assignment of Treatment/Randomization Number 68
8.1.8 Study Intervention Administration 69
8.1.8.1 Timing of Dose Administration 69
8.1.9 Discontinuation and Withdrawal 69
8.1.9.1 Withdrawal From Future Biomedical Research 70
8.1.10 Participant Blinding/Unblinding 70
8.1.11 Domiciling 71
8.1.12 Calibration of Equipment 71
8.2 Efficacy/Immunogenicity Assessments 71
8.3 Safety Assessments 71
8.3.1 Physical Examinations 72
8.3.2 Vital Signs 72
8.3.2.1 Resting Vital Signs 72
8.3.2.2 Orthostatic Vital Signs 73
8.3.3 Electrocardiograms 73
8.3.4 Neurological Exams 74
8.3.5 Mini-Mental State Examination (MMSE-2) 74
8.3.6 WAIS-R Digit Symbol Substitution Test (DSST) 74
8.3.7 Clinical Safety Laboratory Assessments 74
8.3.8 Suicidal Ideation and Behavior Monitoring 75
8.3.8.1 Clinical Assessments for Suicidal Ideation and Behavior Monitoring 75
8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events 75

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information 76
8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events 78
8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information 78
8.4.4 Regulatory Reporting Requirements for SAE 78
8.4.5 Pregnancy and Exposure During Breastfeeding 78
8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs 78
8.4.7 Events of Clinical Interest 78
8.5 Treatment of Overdose 79
8.6 Pharmacokinetics 79
8.6.1 Blood Collection for Plasma MK-1942 79
8.7 Pharmacodynamics 80
8.8 Biomarkers 80
8.8.1 Planned Genetic Analysis Sample Collection 80
8.9 Future Biomedical Research Sample Collection 80
8.10 Visit Requirements 80
8.10.1 Screening 80
8.10.2 Treatment Period Visit 81
8.10.3 Discontinued Participants Continuing to be Monitored in the Study 81
8.10.4 Poststudy 81
8.10.5 Critical Procedures Based on Study Objectives: Timing of Procedure 81
8.10.6 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters 82
9 STATISTICAL ANALYSIS PLAN 83
9.1 Statistical Analysis Plan Summary 84
9.2 Responsibility for Analyses 85
9.3 Hypotheses/Estimation 86
9.4 Analysis Endpoints 86
9.5 Analysis Populations 86
9.6 Statistical Methods 87
9.6.1 Safety 87
9.6.2 Pharmacokinetics 87
9.6.3 General 89
9.7 Interim Analyses 89
9.8 Multiplicity 89
9.9 Sample Size and Power Calculations 90
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 91

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 91
10.1.1 Code of Conduct for Clinical Trials.....91
10.1.2 Financial Disclosure.....93
10.1.3 Data Protection.....93
10.1.3.1 Confidentiality of Data 94
10.1.3.2 Confidentiality of Participant Records.....94
10.1.3.3 Confidentiality of IRB/IEC Information.....94
10.1.4 Publication Policy.....94
10.1.5 Compliance with Study Registration and Results Posting Requirements ...95
10.1.6 Compliance with Law, Audit, and Debarment 95
10.1.7 Data Quality Assurance 96
10.1.8 Source Documents 97
10.1.9 Study and Site Closure.....97
10.2 Appendix 2: Clinical Laboratory Tests.....98
10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.....99
10.3.1 Definition of AE 99
10.3.2 Definition of SAE 100
10.3.3 Additional Events Reported.....101
10.3.4 Recording AE and SAE 101
10.3.5 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor 105
10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation.....106
10.5 Appendix 5: Contraceptive Guidance.....107
10.5.1 Definitions.....107
10.5.2 Contraception Requirements.....108
10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research.....109
10.7 Appendix 7: Country-specific Requirements 114
10.8 Appendix 8: Approximate Blood Volume Table.....115
10.9 Appendix 9: 12-Lead Electrocardiogram Abnormality Criteria 116
10.10 Appendix 10: Algorithm for Assessing Out of Range Laboratory Values ...118
10.11 Appendix 11: The General and Targeted Neurological Exams.....119
10.12 Appendix 12: Additional Information to be Collected from Subjects Who Report Suicidal Ideation and/or Behavior.....125
10.13 Appendix 13: Abbreviations 126
11 REFERENCES.....128

LIST OF TABLES

Table 1 Proposed Dosing Regimens of MK-1942 and Donepezil for the Study 16
Table 2 Summary of the Pharmacokinetic Parameters of MK-1942 Following Administration of Multiple Ascending Oral Doses to Healthy Adult Subjects 25
Table 3 Subjects Reporting Adverse Events (Incidence > 0% in One or More Treatment Groups) 30
Table 4 Calculated CCI [redacted] on the Last Day of Each Dose Level Following Treatment of Healthy Adult Participants with Oral Doses of MK-1942 in Panel B 37
Table 5 Proposed Dosing Regimens for MK-1942-004-001 38
Table 6 Projected Systemic Exposures and Receptor Occupancies Achieved at Steady State with the Proposed Dose Levels. 46
Table 7 Study Interventions.....57
Table 8 Sample Allocation Schedule 59
Table 9 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events 77
Table 10 Pharmacokinetic Sample (Blood) Collection Windows.....82
Table 11 Operating Characteristics for a One AE Incidence Rate.....90
Table 12 Protocol-required Safety Laboratory Assessments 98

LIST OF FIGURES

Figure 1 Timing of Monitoring and Interventions 17
Figure 2 Mean (SD) Plasma Concentration Time Profiles for MK-1942 Following Administration of Multiple Oral Doses to Healthy Adult Subjects in Panels E and F (red) from Study MK-1942-002. (Top; Linear Scale, Bottom; Log-linear Scale) 28
Figure 3 Amelioration of Scopolamine-Induced Cognitive Impairment by an CCI [redacted] 46

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Pharmacokinetics of MK-1942 Administered to Alzheimer's Disease Patients Receiving Donepezil Treatment.

Short Title: MK-1942/Donepezil Interactions in AD Patients

Acronym: DDI

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

The study population consists of Alzheimer Disease (AD) patients with mild to moderate cognitive impairment, 50-85 years of age.

Primary Objectives	Primary Endpoints
- Evaluate the safety and tolerability of treatment (MK-1942 co-administered with donepezil) in AD patients with mild-to-moderate cognitive impairment.	- Safety measures (VS, ECGs, clinical chemistry, hematology, urinalysis, targeted neurological exams, Columbia suicide severity rating scale) and Adverse Event reports
Secondary Objectives	Secondary Endpoints
- Evaluate the effects of donepezil on the PK of MK-1942 in AD patients Hypothesis - The plasma Cmax of MK-1942 determined on the last day of a titrated treatment regimen (Day 21 [28]) when co-administered with donepezil to AD patients is similar to the Cmax obtained following administration of MK-1942 to HEV from MK-1942-004, Panel C. That is, the true GMR (MK-1942 + donepezil in AD / MK-1942 in HEV) is contained within the interval (0.5, 2.0). - Evaluate the effects of MK-1942 on the PK of donepezil in AD patients. Estimation: - Estimate the GMRs of plasma PK parameters (AUC0-24, Cmax) for donepezil before and during administration of donepezil + MK-1942 to AD patients.	- Cmax, AUC0-12, AUC0-24, Ctrough, Tmax, apparent terminal t1/2, CLss/F, and Vzss/F of MK-1942 - AUC0-24, Cmax, Ctrough, Tmax for donepezil

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Alzheimer Disease
Population	AD patients with mild-to-moderate cognitive impairment
Study Type	Interventional
Intervention Model	Single Group This is a multi-site study.
Type of Control	Placebo
Study Blinding	Double-blind
Blinding Roles	Participants or Subjects Investigator Sponsor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 24 weeks from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 24 participants will be allocated/randomized.

Intervention Groups and Duration:

Intervention Groups	<table><tr><th>Intervention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Adminis--tration</th><th>Regimen/ Treatment Period</th><th>Use</th></tr><tr><td>AD Patients</td><td>MK-1942</td><td>1-mg, 5-mg, 10-mg</td><td>BID</td><td>PO</td><td>8-mg BID x 7D; 15-mg BID x 7D; 30-mg BID x 7 D; *50-mg BID x 7D (provisional)*</td><td>Ex-perimen-tal</td></tr><tr><td></td><td>MK-1942 Placebo</td><td>N/A</td><td>BID</td><td>PO</td><td>BID x 21 (28) D</td><td>Ex-perimen-tal</td></tr><tr><td colspan="7">Abbreviations D, day; N/A, not applicable</td></tr></table>
Total Number	1 Arm
Duration of Participation	Each individual will participate in the study for approximately 11 weeks from the time they sign the Informed Consent Form through the final contact. After a screening phase of 5 weeks, each participant will receive the assigned intervention for approximately 4 weeks. After the end of treatment, each participant will be followed for an additional 2 weeks.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Insert Other Oversight Committee	No
There are no governance committees in this study.	

Study Accepts Healthy Volunteers: Yes

A list of abbreviations used in this document can be found in Appendix 13.

1.2 Schema

The study design is depicted in Table 1.

Table 1 Proposed Dosing Regimens of MK-1942 and Donepezil for the Study

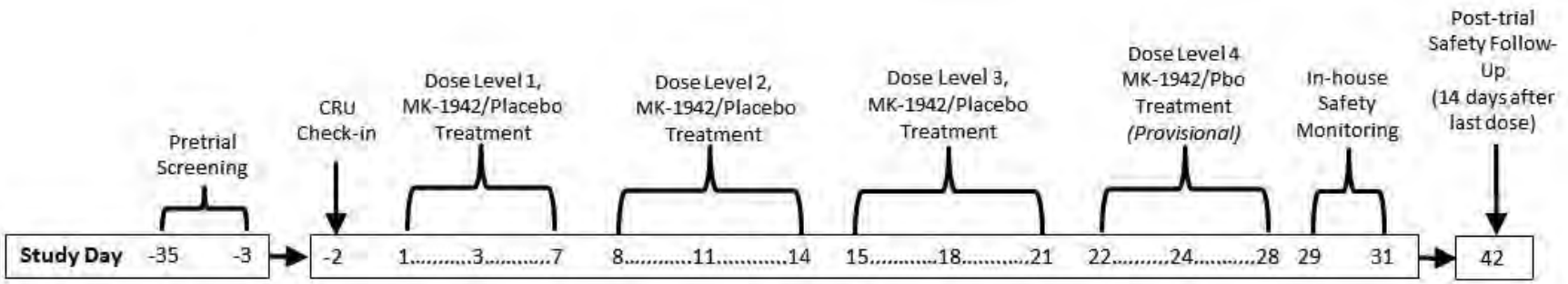
Treatment[a]	**Study Week**			
	1	**2**	**3**	***(4)***
Donepezil (personal prescription)	≥10-mg, ≤15-mg QD x 28 D			
MK-1942/ Placebo	8-mg BID x 7D	15-mg BID x 7D	30-mg BID x 7D[b]	*≤50 -mg BID x 7D*[c] *(Provisional)*

Abbreviations: D, day

a: There will be 18 participants randomized to receive MK-1942 and 6 participants to receive matching placebo. Assignment of participants to their treatments will be determined according to a computer-generated allocation schedule. MK-1942/matching placebo will be administered as a DFC formulation. Refer to Section 6.6 (Dose Modification) for the safety, tolerability and PK data that will be reviewed prior to dose escalation.

b: The doses for Dose Levels 3 and 4 will be based on the safety and tolerability of the highest doses administered in MK-1942-004 (Section 2.2.3). The dose of MK-1942 will not exceed 50-mg BID.

c: The proposed fourth dose level is provisional, pending the results of all available safety, tolerability and PK data from the previous dose-levels.



CRU = Clinical research unit, Pbo = Placebo

Figure 1 Timing of Monitoring and Interventions

1.3 Schedule of Activities

Study Period	**Screening**			**Intervention (Days)[a]**																											**Post-Treatment Safety Monitoring**			**Post-study**
Scheduled Day	**Up to day -35**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**42**
Administrative Procedures																																			
Informed Consent	X																																	
Informed Consent for Future Biomedical Research	X																																	
Participant Identification Card	X																																	
Screening Procedures/Reviews																																		
Medical History	X																																	
Prior/Concomitant Medication Review	X ---------- X																																	
Height (BMI)	X																																	
Weight	X																															X		X
Full physical examination[b]	X		X																													X		X
Full Neurological Examination	X																																	X
HIV, hepatitis B and C screen	X																																	
Follicle Stimulating Hormone (FSH) (females only)	X																																	
Urine Drug Screen[c]	X		X																															
CYP2C19 Genotyping	X																																	
MMSE-2[d]	X																													X				X
DSST[e]	X		X														X													X				X
C-SSRS Baseline/Screening	X																																	

Study Period	**Screening**			**Intervention (Days)[a]**																										**Post-Treatment Safety Monitoring**			**Post-study**
Scheduled Day	**Up to day -35**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**42**
Inclusion/Exclusion Criteria	X			X																														
Domiciling[f]		X----------																														X		
Assignment of allocation number				X																														
Standard Meals[g]		X----------																																X
Treatment Administration																																		
MK-1942 or Placebo Administration[h]				Dose Level 1							Dose Level 2							Dose Level 3						Dose Level 4 (Provisional)										
Donepezil Administration[i]		X ----------																																X
Safety Monitoring																																		
Vital Signs (heart rate, blood pressure, respiratory rate, body temperature)[j,k]	X		X	**X**	X	X	X			**X**	**X**	X	X	X			**X**	**X**	X	X	X			**X**	**X**	X	X	X			**X**	X	X		X
Orthostatic VS (heart rate, blood pressure)[j,l]	X			X						X	X						X	X						X	X						X	X	X		X
12-lead ECG[m]	X			**X**	X	X	X			**X**	**X**	X	X	X			**X**	**X**	X	X	X			**X**	**X**	X	X	X			**X**	X	X		X
Hematology, Chemistry, Urinalysis[n]	X		X								X							X							X							X		X		X
AE/SAE Review	X----------																																		X
Targeted Neurological Examination[o]			X	X			X			X	X			X			X	X			X			X	X			X			X	X			
C-SSRS SLA[p]				X							X							X							X							X		X		X

Study Period	**Screening**			**Intervention (Days)[a]**																										**Post-Treatment Safety Monitoring**			**Post-study**
Scheduled Day	**Up to day -35**	**-2**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**42**
Pharmacokinetic Sampling																																			
Blood for Plasma MK-1942 assay[q]				**X**	X		X			**X**	X	X		X			**X**	X	X		X			**X**	X	X		X			**X**	X	X	X	
Blood for Plasma Donepezil Assay[r]			**X**	X																												**X**	X			
Biomarkers																																			
Blood for Genetic Analysis[s]				X																															

[a] If Dose Level 4 is not administered, procedures scheduled for Days 28-30 should be timed relative to the AM dose administered on Day 21.
[b] PE on Day 30 should be conducted ~ 48 hrs after the last dose administered on Day 28.
[c] May be done upon arrival in the CRU.
[d] Assessments on Day 28 should be given within 12 hours of the last morning dose.
[e] A practice assessment will be administered at screening. The assessment given on Day -1 will provide the baseline value. On Days 14 and 28, assessments should be given within 4 hours after the AM dose. See study operation's manual for specific instructions on test administration.
[f] Patients will be domiciled the entire 21-28 D of treatment, with 4 additional overnight stays (Days -2, -1, 29, 30) for pre-treatment baseline, PK assessments and for post-treatment safety monitoring. Patients may leave the CRU on Days 5, 6 of each dosing level at the discretion of the PI, with at-home safety and compliance monitoring.
[g] Patients may be provided a meal on Day 31 prior to discharge.
[h] Patients will take the first dose of MK-1942/placebo in the AM along with daily donepezil treatment. Patients will be dosed BID with MK-1942/placebo, except on Day 28, when only the morning dose is administered. If Dose Level 4 is not given, only the AM dose of Dose Level 3 will be given on Day 21.
[i] Patients will take their personal donepezil prescription QD in the AM. Those patients who do not take donepezil in the AM should be advised to start morning dosing on Day -7.
[j] VS measures out of normal range will be repeated up to 3 times in 15 minutes, or until measures return to normal.
[k] **Days 1, 7, 8, 14, 15, 21, 22, and 28 are intense monitoring days:** Single measures of semi-recumbent HR and BP to be taken predose (triplicate on Day 1), 2 and 4 hrs after the AM dose. Days -1, 2, 3, 4, 9, 10, 11, 16, 17, 18, 23, 24, and 25: Single measures of HR and BP to be taken predose and ~ 2 hrs after the AM dose. Days 29 and 30: HR and BP to be taken at ~ 24 and 48 hrs postdose relative to Day 28, respectively. Single measures of RR, BT taken predose on Day 1 and ~ 2 hrs after the AM dose on Days 1, 7, 8, 14, 15, 21, 22 and 28.
[l] Days 1, 7, 8, 14, 15, 21, 22, and 28: Orthostatic HR and BP to be taken pre-dose on Day 1 and ~ 2 hrs after the AM dose. Days 29 and 30: orthostatic measures can be taken at ~ 24 and 48 hrs relative to post-dose Day 28.
[m] All ECGs will be measured in triplicate. **Days 1, 7, 8, 14, 15, 21, 22, and 28 are intense monitoring days**: predose and ~ 1, 2, 3, 4, 6, 8,and 12hours after the AM dose. Days 2, 3, 4, 9, 10, 11, 16, 17, 18, 23, 24, and 25: predose and ~ 2 hours after the AM dose. Days 29 and 30: ~ 24 and 48 hrs after the Day 28 dose.
[n] Days -1, 8, 15, 22, and 28: ~ 2 hrs after the AM dose of donepezil. Day 30: ~ 48 hrs after the Day 28 dose.
[o] Days -1, 1: ~ 1.5 hours after AM dose of donepezil. Days 4, 7, 8, 11, 14, 15, 18, 21, 22, 25, and 28: ~ 1.5 hours after AM dose, or more frequently as required by investigator. Day 29: ~ 24 hrs after AM dose Day 28.
[p] Day 1: before AM dose. Days 8, 15, 22, and 28: ~ 4 hrs after the AM dose. Day 30: ~ 48 hrs after the AM dose on Day 28.

Study Period	Screening			Intervention (Days)[a]																										Post-Treatment Safety Monitoring			Post-study
Scheduled Day	Up to day -35	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	42

[q] **Days 1, 7, 14, 21, and 28 are intense PK sampling days.** Blood samples will be taken predose, and at 0.5, 1, 2, 3, 4, 6, and 12 hours post AM dose. On Day 28 (or last day of dosing), administer the AM dose only and sample predose, 0.5, 1, 2, 3, 4, 6, 12, 24, 48, and 72 hr post-dose. On Days 2, 4, 8, 9, 11, 15,16, 18, 22, 23, and 25 a sample will be taken before the AM dose (Ctrough).

[r] **Days -1 and 28 are intense PK sampling days.** Samples to be taken pre-dose and 0.5, 1, 2, 3, 4, 6, 12 and 24 hrs post-dose. On Day -1 time points are relative to the morning donepezil dose. If Dose Level 4 is not given, Day 21 will be the second intense PK sampling day instead of Day 28.

[s] Pre-dose from enrolled participants only – See Section 8.8.

2 INTRODUCTION

CCI [redacted] AD is a progressive neurodegenerative disorder characterized by the loss of neurons from the cerebral cortex and hippocampus, and of cholinergic neurons in the nucleus basalis, CCI [redacted]

CCI [redacted]

2.1 Study Rationale

This study has the following goals: to further explore doses of MK-1942 CCI [redacted] to evaluate the potential for the combinations of MK-1942 and donepezil to increase the incidence or severity of AEs characteristic of either agent, or the appearance of new ones; to observe any effects of the combination of donepezil and MK-1942 on the PK of either agent in AD patients.

Regarding these interactions, previous clinical studies indicate that the primary AEs observed following MK-1942 administration are dizziness, headache and nausea of mild to moderate severity, with infrequent reports of gait abnormalities, visual disturbances, and emesis. Some of these symptoms are held in common with the AE profile of donepezil, which is characterized by nausea, dizziness, diarrhea, emesis, muscle cramps, fatigue, bradycardia and syncope. Because the incidence and/or severity of these AEs may be aggravated upon co-administration of donepezil with MK-1942, the possibility of such an interaction will be evaluated by administering a potentially efficacious dosing regimen of MK-1942 to a panel of AD patients stably maintained on donepezil (≥10-mg, ≤15-mg) as part of their treatment for cognitive impairment.

In addition to the potential effects of MK-1942 and donepezil co-administration, patients with AD frequently exhibit unsteady gait, contributing to an increased propensity for falls [O'Keeffe, S. T., et al 1996]. The incidence of falls may be worsened by MK-1942 treatment at efficacious dose levels due to increased episodes of dizziness and/or gait disturbances. Therefore, administering MK-1942 to a population of AD patients receiving donepezil is

justified for determining whether an interaction of the two drugs may alter their general tolerability or PK.

2.2 Background

Refer to the IB for detailed background information on MK-1942.

2.2.1 Pharmaceutical and Therapeutic Background

CCI [redacted]

When administered to rhesus monkeys in the scopolamine-impaired object retrieval assessment, MK-1942 improved cognitive performance CCI [redacted]. These effects on cognition are consistent with those observed with other, structurally diverse CCI [redacted], both across species (mice, rats, rhesus and African Green monkeys) and cognitive domains (attention, working memory, episodic memory and executive function).

2.2.2 Preclinical and Clinical Studies

Please refer to the Investigator's Brochure for detailed information on the preclinical and clinical studies to date involving MK-1942.

2.2.3 Ongoing Clinical Studies

2.2.3.1 MK-1942-002: A Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study of the Safety, Tolerability and Pharmacokinetics of MK-1942 in Healthy Participants

MK-1942-002 evaluated the safety and PK of multiple oral doses of MK-1942 CCI [redacted].

Participants are being randomized to one of 6 panels, with active and placebo treatments being administered in a 3:1 ratio. CCI [redacted]

The Cmax and AUC values achieved in this study using the DFC formulation were generally consistent with those reached in MK-1942-001 with the OSF at comparable dose levels. CCI [redacted] Accumulation was consistent with the apparent terminal CCI [redacted] hours, indicating that the PK of MK-1942 is not time dependent.

Plasma concentrations associated with the highest dosing levels (Panels E, F) [Figure 2] were generally consistent with the BID dosing data from previous panels. CCI [redacted]

Table 2 Summary of the Pharmacokinetic Parameters of MK-1942 Following Administration of Multiple Ascending Oral Doses to Healthy Adult Subjects

CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

Figure 2 Mean (SD) Plasma Concentration Time Profiles for MK-1942 Following Administration of Multiple Oral Doses to Healthy Adult Subjects in Panels E and F (red) from Study MK-1942-002. (Top; Linear Scale, Bottom; Log-linear Scale)

Of the 48 total participants treated in Panels A-F, 42 reported one or more AEs. One participant experienced 2 episodes of moderate nausea lasting 3 hours and 15 minutes, and 2 cases of vomiting lasting 5 and 10 minutes on days 3 and 4 of dosing. This individual withdrew consent for additional dosing but completed the remainder of the study monitoring tasks and follow-up. The second participant experienced one episode of moderate nausea lasting 15.5 hours accompanied by 10 minutes of vomiting on day 4 of dosing. This was followed on day 5 of dosing by an episode of mild nausea lasting 17.2 hours. This individual continued the dosing regimen and completed the study. Otherwise, the treatment has been safe and generally well-tolerated, with no clinically significant, treatment-related abnormalities in: VS (HR, SBP, DBP, RR, BT); ECG; blood chemistry; hematology; neurological exams; physical exams; or behavior (suicidality). The most commonly reported AEs (≥2 subjects) due to all causes are: dizziness (20), headache (17), nausea (9), nasopharyngitis (5), diarrhea (4), sensory processing disorder (4), abdominal pain (4), vomiting (3), increased SBP (2), dry mouth (2) palpitations (2), abdominal discomfort (2), dizziness postural (2), hot flush (2), and neutropenia (2) [Table 3].

The incidence and severity of dizziness episodes appeared to decrease with repeated administration over 5-10 days at a given dose level. CCI

CCI [redacted] These results suggest that tolerance to dizziness and headache could be elicited by titrating doses of MK-1942 by BID administration over 7 days/dose level.

Table 3 Subjects Reporting Adverse Events (Incidence > 0% in One or More Treatment Groups)

	Screening		Panel A		Panel B		Panel C		Panel D	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	48		8		8		8		8	
with one or more adverse events	1	(2.1)	5	(62.5)	6	(75.0)	6	(75.0)	5	(62.5)
with no adverse events	47	(97.9)	3	(37.5)	2	(25.0)	2	(25.0)	3	(37.5)
Blood and lymphatic system disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Eosinophilia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Neutropenia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Cardiac disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Palpitations	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Supraventricular extrasystoles	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Eye disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**	**0**	**(0.0)**
Vision blurred	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)
Gastrointestinal disorders	**0**	**(0.0)**	**2**	**(25.0)**	**2**	**(25.0)**	**0**	**(0.0)**	**3**	**(37.5)**
Abdominal discomfort	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Abdominal pain	0	(0.0)	1	(12.5)	1	(12.5)	0	(0.0)	0	(0.0)
Diarrhoea	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Dry mouth	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Dyspepsia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nausea	0	(0.0)	1	(12.5)	1	(12.5)	0	(0.0)	1	(12.5)
Vomiting	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
General disorders and administration site conditions	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**	**0**	**(0.0)**	**0**	**(0.0)**
Chest discomfort	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

SUBJECTS WITH ADVERSE EVENTS
(INCIDENCE > 0% IN ONE OR MORE TREATMENT GROUPS)

	Panel E		Panel F		Placebo		Follow-Up	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	8		8		8		48	
with one or more adverse events	6	(75.0)	6	(75.0)	8	(100.0)	1	(2.1)
with no adverse events	2	(25.0)	2	(25.0)	0	(0.0)	47	(97.9)
Blood and lymphatic system disorders	**0**	**(0.0)**	**1**	**(12.5)**	**0**	**(0.0)**	**1**	**(2.1)**
Eosinophilia	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)
Neutropenia	0	(0.0)	1	(12.5)	0	(0.0)	1	(2.1)
Cardiac disorders	**2**	**(25.0)**	**1**	**(12.5)**	**0**	**(0.0)**	**0**	**(0.0)**
Palpitations	1	(12.5)	1	(12.5)	0	(0.0)	0	(0.0)
Supraventricular extrasystoles	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)
Eye disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Vision blurred	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gastrointestinal disorders	**3**	**(37.5)**	**5**	**(62.5)**	**1**	**(12.5)**	**0**	**(0.0)**
Abdominal discomfort	0	(0.0)	1	(12.5)	1	(12.5)	0	(0.0)
Abdominal pain	0	(0.0)	2	(25.0)	0	(0.0)	0	(0.0)
Diarrhoea	2	(25.0)	1	(12.5)	0	(0.0)	0	(0.0)
Dry mouth	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)
Dyspepsia	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)
Nausea	2	(25.0)	4	(50.0)	0	(0.0)	0	(0.0)
Vomiting	2	(25.0)	0	(0.0)	0	(0.0)	0	(0.0)
General disorders and administration site conditions	**0**	**(0.0)**	**2**	**(25.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Chest discomfort	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)

SUBJECTS WITH ADVERSE EVENTS
(INCIDENCE > 0% IN ONE OR MORE TREATMENT GROUPS)

	Screening		Panel A		Panel B		Panel C		Panel D	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**	**0**	**(0.0)**	**0**	**(0.0)**
Chest pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Gait disturbance	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)
Infections and infestations	**0**	**(0.0)**	**1**	**(12.5)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Nasopharyngitis	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)
Pharyngitis	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Injury, poisoning and procedural complications	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**
Contusion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Procedural pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Investigations	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**	**0**	**(0.0)**
Blood potassium increased	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)
Blood pressure diastolic increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Blood pressure systolic increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Electrocardiogram QRS complex prolonged	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**	**1**	**(12.5)**
Back pain	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)
Muscular weakness	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Musculoskeletal stiffness	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Neck pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

SUBJECTS WITH ADVERSE EVENTS
(INCIDENCE > 0% IN ONE OR MORE TREATMENT GROUPS)

	Panel E		Panel F		Placebo		Follow-Up	
	n	(%)	n	(%)	n	(%)	n	(%)
General disorders and administration site conditions	**0**	**(0.0)**	**2**	**(25.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Chest pain	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)
Gait disturbance	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Infections and infestations	**1**	**(12.5)**	**1**	**(12.5)**	**3**	**(37.5)**	**0**	**(0.0)**
Nasopharyngitis	1	(12.5)	0	(0.0)	3	(37.5)	0	(0.0)
Pharyngitis	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)
Injury, poisoning and procedural complications	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Contusion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Procedural pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Investigations	**1**	**(12.5)**	**1**	**(12.5)**	**1**	**(12.5)**	**0**	**(0.0)**
Blood potassium increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Blood pressure diastolic increased	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)
Blood pressure systolic increased	1	(12.5)	0	(0.0)	1	(12.5)	0	(0.0)
Electrocardiogram QRS complex prolonged	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)
Musculoskeletal and connective tissue disorders	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(25.0)**	**0**	**(0.0)**
Back pain	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Muscular weakness	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)
Musculoskeletal stiffness	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Neck pain	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)

SUBJECTS WITH ADVERSE EVENTS
(INCIDENCE > 0% IN ONE OR MORE TREATMENT GROUPS)

	Screening		Panel A		Panel B		Panel C		Panel D	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Nervous system disorders	**0**	**(0.0)**	**3**	**(37.5)**	**5**	**(62.5)**	**5**	**(62.5)**	**3**	**(37.5)**
Balance disorder	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dizziness	0	(0.0)	3	(37.5)	5	(62.5)	3	(37.5)	2	(25.0)
Dizziness postural	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)
Head discomfort	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Headache	0	(0.0)	1	(12.5)	2	(25.0)	4	(50.0)	1	(12.5)
Sensory disturbance	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)
Sensory processing disorder	0	(0.0)	0	(0.0)	1	(12.5)	1	(12.5)	0	(0.0)
Somnolence	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Tunnel vision	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Psychiatric disorders	**0**	**(0.0)**	**1**	**(12.5)**	**1**	**(12.5)**	**0**	**(0.0)**	**0**	**(0.0)**
Listless	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)	0	(0.0)
Staring	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)
Renal and urinary disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**
Leukocyturia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Nocturia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**1**	**(2.1)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**	**0**	**(0.0)**
Nasal congestion	1	(2.1)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**2**	**(25.0)**
Eczema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)
Pruritus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)

SUBJECTS WITH ADVERSE EVENTS
(INCIDENCE > 0% IN ONE OR MORE TREATMENT GROUPS)

	Panel E		Panel F		Placebo		Follow-Up	
	n	(%)	n	(%)	n	(%)	n	(%)
Nervous system disorders	**4**	**(50.0)**	**6**	**(75.0)**	**4**	**(50.0)**	**0**	**(0.0)**
Balance disorder	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)
Dizziness	1	(12.5)	6	(75.0)	0	(0.0)	0	(0.0)
Dizziness postural	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)
Head discomfort	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Headache	3	(37.5)	3	(37.5)	3	(37.5)	0	(0.0)
Sensory disturbance	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Sensory processing disorder	0	(0.0)	2	(25.0)	0	(0.0)	0	(0.0)
Somnolence	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)
Tunnel vision	0	(0.0)	1	(12.5)	0	(0.0)	0	(0.0)
Psychiatric disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Listless	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Staring	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Renal and urinary disorders	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**	**0**	**(0.0)**
Leukocyturia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Nocturia	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)
Respiratory, thoracic and mediastinal disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Nasal congestion	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Skin and subcutaneous tissue disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**
Eczema	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Pruritus	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

SUBJECTS WITH ADVERSE EVENTS
(INCIDENCE > 0% IN ONE OR MORE TREATMENT GROUPS)

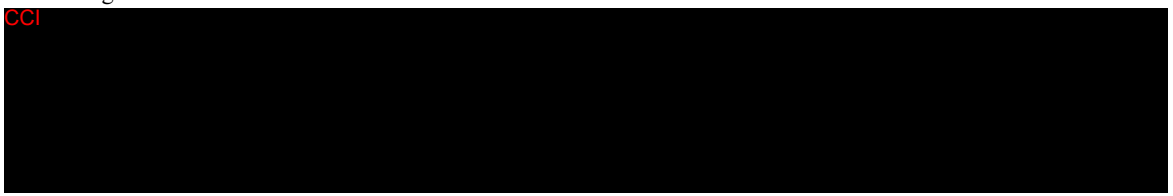
	Screening		Panel A		Panel B		Panel C		Panel D	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Vascular disorders	**0**	**(0.0)**	**0**	**(0.0)**	**0**	**(0.0)**	**1**	**(12.5)**	**0**	**(0.0)**
Haematoma	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)
Hot flush	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hypertension	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Orthostatic hypotension	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

SUBJECTS WITH ADVERSE EVENTS
(INCIDENCE > 0% IN ONE OR MORE TREATMENT GROUPS)

	Panel E		Panel F		Placebo		Follow-Up	
	n	(%)	n	(%)	n	(%)	n	(%)
Vascular disorders	**1**	**(12.5)**	**1**	**(12.5)**	**2**	**(25.0)**	**0**	**(0.0)**
Haematoma	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Hot flush	1	(12.5)	1	(12.5)	0	(0.0)	0	(0.0)
Hypertension	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)
Orthostatic hypotension	0	(0.0)	0	(0.0)	1	(12.5)	0	(0.0)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

CCI



QD=once a day; BID=twice a day
Adverse event terms are from MedDRA Version 22.0

Source: [P002V01MK1942: adam-adsl; adae]

CCI

2.2.3.2 MK-1942-004: A Randomized, Double Blind, Placebo-Controlled Investigation of the Safety, Tolerability and Pharmacokinetics of Multiple-Dose Regimens of MK-1942 in Healthy Elderly Participants

MK-1942-004 is a study of the safety and PK of MK-1942 when administered as multiple dose regimens. The study consists of 3 panels, with Panels A and C each comprised of 8 healthy elderly participants of both genders and Panel B consisting of 8 healthy adults of both genders receiving either MK-1942 (N=6) or placebo (N=2). Participants will be enrolled in only one panel of the study. All participants are domiciled during the treatment period (Panel A: 21 days, Panels B and C: up to 28 days) and for 2 days after completion of dosing for safety monitoring (Table 5). The study will employ multiple dose and titration dosing regimens of varying dose levels (not to exceed 50-mg), dosing frequencies (not to exceed BID) and dosing durations (up to 28 days in total).

Table 5 Proposed Dosing Regimens for MK-1942-004-001

Panel	**A**			**PK Break**	**B**				**PK Break**	**C**			
Treatment	5-mg BID x 7D	10-mg BID x 7 D	20-mg BID x 7D	3 weeks	8-mg BID x 7D	15-mg BID x 7D	30-mg BID x 7D	50-mg BID x 7D	3 weeks	8-mg BID x 7D	15-mg BID x 7D	30-mg BID x 7D	50-mg BID x 7D
Abbreviations: BID= bis-in-diem (twice daily); D=day; PK= pharmacokinetics													

As of 4 March, 2020, 8 subjects in Panel A completed the dosing regimen outlined in Table 5. In addition, 8 healthy adult subjects underwent treatment in Panel B. Although data from both panels remains under blind, no SAEs or discontinuations were reported from panel A. Those AEs reported, primarily lightheadedness and headache, are reversible and of mild severity. Of the 8 subjects in Panel B, 3 individuals reported multiple episodes of dizziness, headache and tinnitus of mild severity during treatment at dose level 2 (15 mg ID/pbo, days 8-14 of treatment). Two of the three individuals continued dosing at 15 mg ID/pbo for an additional week (days 15-21 of treatment) in lieu of escalation to dose level 3, 30 mg ID/pbo. After completing the second week of treatment with 15 mg ID/pbo, both participants withdrew themselves from the study (day 22 of treatment). The third subject withdrew from the study on day 15 of treatment after having received one additional dose of 15 mg. None of these 3 participants met individual stop dosing criteria for the severity of dizziness or nausea. The remaining 5 participants completed all 4 dose levels up to 50 mg ID/pbo. A single episode each of drowsiness and lightheadedness were reported by 2 of those subjects at dose level 3 (30 mg ID/pbo). The same two subjects each reported a single episode of lightheadedness and headache at dose level 4 (50 mg ID/pbo). One subject reported a brief (5 min) episode of emesis on day 23 of treatment at dose level 4, but continued dosing at this level until to the end of the study.

Overall, there were no clinically significant changes in VS, ECG, targeted neurological exams, lab chemistry, hematology or urinalyses manifested by any participant at any point during the study. There were no SAEs or severe, non-serious AEs observed. Stop dosing criteria were not achieved during Panels A, B. Enrollment of Panel C is initiating using the dosing regimen described in Table 5.

2.2.4 Information on Other Study-related Therapy

Donepezil Hydrochloride (HCl)

Donepezil HCl is an AChEI that is marketed for symptomatic treatment of mild-to-moderate cognitive impairment associated with AD. The standard oral dose of donepezil HCl is one 10 -mg tablet daily. The most common AEs associated with donepezil HCl administration (occurring at a frequency of ≥ 5% and at twice the placebo rate at the 10-mg QD dose) are consistent with its cholinomimetic effects and include nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue and anorexia. These AEs are mild in intensity and transient, typically resolving with continued donepezil HCl treatment without the need for dose adjustment [Jackson, S., et al 2004]. Less commonly observed AEs include depression and sleep disturbances (eg, abnormal dreams and somnolence).

Donepezil HCl is ~96% bound to human plasma proteins over the concentration range of 2 to 1000 ng/mL. It is extensively metabolized by the CYP 450 isoenzymes 2D6 and 3A4, undergoes glucuronidation, and is excreted in the urine as the parent compound, four major metabolites (two of which are known to be active), and several incompletely identified, minor metabolites. Donepezil HCl has a Tmax of ~3 to 4 hours and half-life ~70 hours.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical trials will directly benefit from treatment during participation as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

Details of the hypotheses to be tested can be found in Section 9.3.

Objectives	Endpoints
Primary	
• Evaluate the safety and tolerability of treatment (MK-1942 co-administered with donepezil) in AD patients with mild-to-moderate cognitive impairment.	• Safety measures (VS, ECGs, clinical chemistry, hematology, urinalysis, targeted neurological exams, Columbia suicide severity rating scale) and Adverse Event reports
Secondary	
• Evaluate the effects of donepezil on the PK of MK-1942 in AD patients Hypothesis o The plasma Cmax of MK-1942 determined on the last day of a titrated treatment regimen (Day 21 [28]) when co-administered with donepezil to AD patients is similar to the Cmax obtained following administration of MK-1942 to HEV from MK-1942-004, Panel C. That is, the true GMR (MK-1942 + donepezil in AD / MK-1942 in HEV) is contained within the interval (0.5, 2.0).	• Cmax, AUC0-12, AUC0-24, Ctrough, Tmax, apparent terminal t1/2, CLss/F, and Vzss/F of MK-1942 • AUC0-24, Cmax, Ctrough, Tmax for donepezil

Objectives	Endpoints
• Evaluate the effects of MK-1942 on the PK of donepezil in AD patients. Estimation: o The true GMRs of plasma PK parameters (AUC0-24, Cmax) for donepezil before and during administration of donepezil + MK-1942 to AD patients will be estimated.	
Tertiary/Exploratory	
• Evaluate the changes in cognitive function of AD patients by comparing the MMSE-2 and DSST scores obtained at baseline with those from the last day of dosing. • Explore the relationship between plasma concentrations of MK-1942 and corrected QT intervals. • CCI [redacted] • Explore the relationships between genetic variation, response to the treatment(s) administered, and mechanisms of disease. Variation across the human genome may be analyzed for association with clinical data collected in the study.	• MMSE-2 scores • DSST scores • QTcF • Germline genetic variation

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, multi-site, double-blinded study of the safety, tolerability and PK of MK-1942 when co-administered with donepezil. Specifically, the study will evaluate the safety and PK of a selected MK-1942 titration dosing regimen administered to AD patients with mild cognitive impairment currently being treated with a stable dose of donepezil (≥10-mg, ≤15-mg QD).

Participants will be domiciled starting 2 days before treatment, during the MK-1942 treatment period (up to 28 days) and for 3 days after completion of dosing for safety monitoring and PK sampling (Table 1, see Section 1.3, SoA). Participants may elect to spend days 5 and 6 of each dose level at home with concurrence of the PI. Safety and PK

monitoring will be conducted throughout the domiciled treatment period and post-treatment follow-up, with safety ensured by monitoring AEs, VS, 12-lead ECGs, as well as conducting lab safety tests, neurological examinations, PE, and administering the C-SSRS at the times indicated (see Section 1.3). The precise timing of ECGs, blood sampling for PK, clinical and hematology labs and/or other procedures listed in Section 1.3 may be altered at any time during the study based on newly available data. Participants who elect to spend time at home will be monitored at home by telephone to record AE episodes and treatment compliance.

The study will employ titration dosing regimens of varying dose levels (not to exceed 50-mg), dosing frequencies (not to exceed BID) and dosing durations (up to 28 days in total) (Table 1, Figure 1). The decision to titrate doses upwards within a panel and to proceed to subsequent panels will be made by the investigator with mutual agreement from the Sponsor based on all available safety and PK information from previous dose levels.

The doses of MK-1942 proposed for administration may be adjusted in terms of dose level, dosing frequency or duration, within the limits described above. Details of the decision-making process informing dose escalation are provided in Section 6.6.

Because this is a Phase 1 assessment of MK-1942 in humans, the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is therefore written with flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Refer to Section 8.11.6 for examples of modifications permitted within the protocol parameters.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

The objectives of this study include determining if the combination of MK-1942 with donepezil increases the incidence or severity of AEs previously reported for these agents, or results in unanticipated AEs in the patient population targeted for MK-1942 treatment. In addition, any changes in the PK parameters of either MK-1942 or donepezil as a result of co-administration will be assessed.

The study will investigate the effects on safety and PK of co-administration of MK-1942 to AD patients with mild-to-moderate cognitive impairment who are under stable treatment with a treatment regimen of donepezil (≥10-mg, ≤15-mg). CCI [redacted] Participants will be domiciled for the

duration of treatment with the combination of donepezil and MK-1942/placebo in order to ensure adequate safety monitoring and treatment compliance.

4.2.1 Rationale for Endpoints

4.2.1.1 Safety Endpoints

The safety and tolerability of MK-1942 when administered in the multiple dose regimens proposed will be monitored throughout the study by collecting the following safety endpoints: direct assessment/reporting of AEs; physical and neurological exams; C-SSRS endpoints; semi-recumbent and orthostatic VS measures (SBP, DBP, HR, RR, BT); 12-lead ECG parameters; and laboratory safety tests (serum chemistry, hematology, and urinalysis). Clinically meaningful changes in VS and ECGs were not observed in studies MK-1942-001, MK-1942-002 and MK-1942-003 (See MK-1942 IB). However, dizziness, headache, nausea and emesis of mild to moderate severity lasting <24 hours were observed following MK-1942 administration and will be monitored using AE reports, direct observation and targeted neurological exams, including gait assessments taken ~2 hours post-dosing. Monitoring the incidence and severity of episodes of dizziness and the application of stopping criteria, as well as evidence for the development of tolerance to the induction of dizziness by MK-1942, will form the basis for careful escalation between dose levels, thereby minimizing the safety risks for subjects participating in this study. The stopping rules, based on observations of dizziness, nausea and emesis (Section 7.1.1), will be applied to the group on a per-panel and individual within-panel basis.

ECG and VS monitoring will be scheduled in proximity to the Cmax [redacted] after each dose and for up to 2 weeks after the last dose. Prior to starting treatment on Day 1, baseline VS parameters will be recorded in triplicate (Section 8.0) and the average of each parameter will serve as a baseline for comparison to subsequently recorded VS parameters. The relationship between the plasma concentration of MK-1942 and ECG parameters (including QTc) will be assessed as an exploratory objective.

The C-SSRS prospective assessment of suicidal ideation and behavior will be included in this study in compliance with the 2012 FDA guidance requiring prospective assessment in clinical trials conducted under IND applications and trials that are intended for submission in a NDA to the Neurology or Psychiatry Divisions of the FDA or biologics license application, as well as assessment in trials that fall within the guidance for other reasons (eg, CNS active/penetrant compounds, and known mechanisms or indications for which suicidal ideation/behavior has been previously identified as a potential concern). The Baseline/Screening version of the C-SSRS will be administered at screening, while the Since Last Assessment version of the C-SSRS/SLA will be given at several points during and after treatment administration to all subjects enrolled, including at the Post-trial visit (see Section 8.0).

In addition to regular safety monitoring conducted during the treatment period, subjects will remain in the clinic for three additional days of post-dose safety monitoring and PK sampling at the end of the treatment period (Section 8.0). This post-treatment period allows for plasma

MK-1942 levels to decline so that any changes in C-SSRS endpoints resulting from a decrease in exposure may be manifested.

Additional details on the safety and toxicology of MK-1942 as determined in preclinical investigations are provided in the MK-1942 IB. In summary, CV and respiratory safety studies in monkeys, rats and guinea pigs noted no significant changes in VS or ECG parameters following exposures to MK-1942 in excess of those anticipated following projected efficacious doses.

In summary, preclinical toxicology as well as clinical safety findings for MK-1942 suggest that it will be safe, CCI [redacted] at steady state for the highest dose proposed in this investigation (50-mg BID). Nonetheless, the incidence and severity of AEs observed following direct reports and targeted neurological exams will be recorded at multiple timepoints during the study to aid in dose escalation decisions.

Pharmacokinetic Endpoints

The plasma PK of MK-1942 following multiple dose co-administration with donepezil will be characterized by determining the Cmax, Tmax, Ctrough, and AUC0-12 after the first dose. In addition, Cmax, Tmax, Ctrough, AUC0-12, AUC0-24, apparent terminal t1/2, CLss/F, Vzss/F and accumulation ratio will be determined at steady state. This will allow doses and dosing regimens in elderly participants with AD to be identified that produce systemic exposures in the predicted efficacious range CCI [redacted] while providing insights into the ability of donepezil to alter the PK of MK-1942.

Similarly, the plasma PK of donepezil following once daily administration will be characterized by determining the Cmax, Tmax, and AUC0-24 on the day before administration of the first dose of MK-1942 and after 21 (28) days of co-administration. Determining the Cmax and AUC0-24 of donepezil during co-administration with MK-1942 will provide insights into the ability of MK-1942 to alter the PK of donepezil.

Exploratory Endpoints

The Mini-Mental State Exam, edition 2 (MMSE-2) will be administered to AD patients at screening and upon completion of up to 28 days of treatment. The score from the MMSE-2 given at screening will be used as an inclusion criterion, to ensure that AD patients being enrolled fall into the cognitive impairment categories of mild to moderate severity. The MMSE-2 is a 30-point examination evaluating Registration, Orientation to Time, Orientation to Place, Attention, Recall, Language, Repetition, Complex Commands, and Recall tasks. A score between 21 to 26 typically indicates that a subject is experiencing mild cognitive impairment, while scores in the range of 10-20 are indicative of patients with moderate cognitive impairment. This study proposes to enroll individuals with mild to moderate cognitive impairment as indicated by scores between 17 to 26. This range will allow for broader recruitment while reducing the burden on CRU personnel associated with caring for patients with MMSE-2 scores < 17. In addition to its use as a screening tool for identifying

candidate participants as having mild to moderate cognitive impairment, the MMSE-2 will be used as an exploratory endpoint to determine whether the treatment regimen results in any changes from the initial score.

The WAIS-R Digit Symbol Substitution Test (DSST) is a test of processing speed and working memory. The DSST will be used in this study as an exploratory endpoint for rapidly assessing whether treatment enhances cognition, as well as a safety signal for the development of treatment-induced cognitive decline. DSST scores from tests administered at the middle and the end of the study will be compared to the baseline score to determine if treatment has any effect on cognitive function.

4.2.1.2 Planned Exploratory Biomarker Research

4.2.1.2.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome. Analysis may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

CCI [redacted]

4.2.1.3 Future Biomedical Research

The Sponsor will conduct future biomedical research on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (ribonucleic acid [RNA]), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of future biomedical research are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator/Placebo

Placebo will be used in this trial to allow for an appropriate assessment of the safety data of MK-1942, any impact of MK-1942 treatment on donepezil PK, and to maintain study blinding to reduce bias.

4.2.3 Rationale for Suicidal Ideation and Behavior Monitoring

Prospective assessment of suicidal ideation and behavior will be performed in this study using the C-SSRS. This assessment is being conducted in compliance with the 2012 FDA guidance requiring prospective assessment in clinical studies conducted under IND applications and studies that are intended for submission in a NDA to the Neurology or Psychiatry Divisions of the FDA or biologics license application, as well as assessment in studies that fall within the guidance for other reasons (eg, CNS active/penetrant compounds, and known mechanisms or indications for which suicidal ideation/behavior has been previously identified as a potential concern).

4.3 Justification for Dose

The rationales for the doses and estimated exposures are detailed in Sections 4.3.1 and 4.3.2.

As this is a Phase 1 assessment of MK-1942 in humans, and the PK, PD and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants. Details of allowed modifications are provided in Section 8.11.6.

4.3.1 Starting Dose for This Study

The study starts by administering 8-mg MK-1942/placebo BID for 7 days. This dose level was well-tolerated in study MK-1942-002, CCI [redacted], similar to those observed after a single 12-mg dose. When this dose level followed administration of 5-mg BID x 7D in Panel D of PN002, it was associated with 4 episodes of the non-serious AEs of dizziness and headache/head discomfort of mild severity, resolving in <6 hours. Because the AEs observed with the 8-mg BID dose were mild and reversible and the frequency and severity of these episodes declines with repeated dosing over 7 days, this dose level is considered a suitable start for the titration

dosing regimen proposed for this investigation, where each dose level increases in increments of approximately 2-fold.

4.3.2 Maximum Dose/Exposure for This Study

Preclinical investigations with an CCI analog of MK-1942 indicate that the cognitive performance of scopolamine-impaired NHP in the object retrieval assay are maximized following a repeat dosing regimen that achieves steady-state plasma concentrations CCI Given that the equivalent doses may be required for clinically significant levels of efficacy, an objective of this study is to determine the safety and tolerability of donepezil/MK-1942 co-administration using doses of MK-1942 CCI (Table 6). The exploration of doses of MK-1942 CCI is supported by the relative safety and tolerability of doses of 20-mg CCI when administered in previous investigations using a titration dosing regimen (see Section 2.2.3.1.).

CCI

Figure 3 Amelioration of Scopolamine-Induced Cognitive Impairment CCI

Table 6 Projected Systemic Exposures and Receptor Occupancies Achieved at Steady State with the Proposed Dose Levels.

CCI

Because the PK parameters of MK-1942 increase linearly in a dose-dependent fashion, data from protocol MK-1942-002 (Table 2, Section 2.2.3) was used to project the steady-state exposures obtained following administration of higher doses of MK-1942 than previously administered, assuming that MK-1942 PK is similar in elderly and non-elderly subjects. CCI [redacted]. Moreover, the 50-mg dose will only be administered if the 30-mg BID x 7D dose level is found to be safe and well tolerated, as defined by the stop dosing criteria (see Section 6.6.1). Finally, if the 50-mg dose is not tolerated by participants in MK-1942-004, Panels B and C, this dose will not be administered in the provisional dose level period.

4.3.3 Rationale for Dose Interval and Study Design

MK-1942 is being developed as an adjunct to current therapies (eg, AChEI) for the treatment of cognitive impairment associated with Alzheimer's dementia. The intent of this investigation is to evaluate the safety, tolerability and PK of MK-1942 when combined with the most commonly prescribed AChEI, donepezil in AD patients. Doses of donepezil appropriate for treating cognitive impairment associated with AD will be co-administered with a dosing regimen of MK-1942 projected to achieve potentially efficacious receptor occupancies CCI [redacted]. These RO values are based on observations of the ability of MK-1942 CCI [redacted] to reverse cognitive impairment in preclinical models (object retrieval performance in scopolamine-impaired NHP). The proposed regimen will also help to establish MK-1942 dosing margins for a safe treatment regimen.

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Clinical investigation MK-1942-002 (Section 2.3.3) indicated that administration of MK-1942 BID over at least 7 days was associated with a decrease in the incidence of episodes of dizziness, headache and other AEs. This tolerance to the adverse effects of MK-1942 was typically manifested after at least 5 days of dosing.

In summary, this study proposes the co-administration of MK-1942 with donepezil, using a titration dosing regimen of MK-1942 BID for 7 days per dose level, with a maximum dose level of 50-mg [redacted]

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

A study may be paused during review of newly available preclinical/clinical safety, PK, pharmacodynamic, efficacy, or biologic data or other items of interest, prior to a final decision on continuation or termination of the study. It may be necessary to keep the study open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the study. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. If the decision has been made to end the study following this review period, the study end will be defined as the date of the Sponsor decision, and this end of study date supersedes the definitions outlined above. The Competent Authority(ies) and IRB(s)/IEC(s) will be apprised of the maximum duration of the study beyond the last participant out and the justification for keeping the study open.

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

An objective of this early Phase 1 study is to identify a safe and well-tolerated dosing regimen that achieves the PK, PD, and/or biologic targets in humans based on preclinical or early clinical data. Therefore, it is possible that study participants may not receive all doses specified in the protocol if this objective is achieved at lesser dose levels. This would not be defined as early termination of the study, but rather an earlier than anticipated achievement of the study objective(s). If a finding (eg, PK, pharmacodynamic, safety, etc.) from another preclinical or clinical study using the study intervention(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this study results in the study(s) or program being stopped for non-safety reasons, this also does not meet the definition of early study termination.

Early study termination is defined as a permanent discontinuation of the study due to unanticipated concerns of safety to the study participants arising from clinical or preclinical studies with the study intervention(s), comparator(s), drug(s) of the same class, or methodology(ies) used in this study.

5 STUDY POPULATION

Men and WONCBP with mild-to-moderate cognitive impairment associated with AD and between the ages of 50-85 (inclusive) will be enrolled this study. The degree of cognitive impairment in these candidates will be determined based on their MMSE-2 score (17-26) taken at screening. There should be no more than ~17 (~70%) patients with MMSE-2 scores consistent with mild cognitive impairment (21-26) enrolled in the trial. Similarly, there should be no less than ~7 (~30%) patients with MMSE-2 scores consistent with moderate cognitive impairment (17-20) enrolled in the trial.

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

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

1. Have a BMI $\geq$ 18 and $\leq$35 kg/m^2, inclusive. See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI = weight (kg)/height (m)^2.

2. Is in good health based on medical history, physical examination, VS measures and ECG performed prior to randomization.

    - Participants with chronic medical conditions, including but not limited to hypertension, hyperlipidemia, diabetes (Type 1 or 2) or hypothyroidism, which have been well-controlled on a stable dose of medication for the past two months and who are not receiving any proscribed medications for treatment may be enrolled if clinically acceptable to the investigator and Sponsor.

    Section 10.8, Appendix 8 provides a table of 12-Lead ECG Abnormality Criteria.

3. Is in good health based on laboratory safety tests obtained at the screening visit. Appendix 10.2 provides a table of laboratory safety tests to be performed. Appendix 10.10 provides an algorithm for the assessment of out of range laboratory values.

4. Have a negative UDS prior to randomization.

5. Report a history of cognitive and functional decline with gradual onset and slow progression for at least one year before Screening, that is either corroborated by an informant who knows the subject well or is documented in medical records.

6. Have a MMSE-2 score $\geq$17 to $\leq$26 at Screening, as confirmed by the investigator. The MMSE-2 should be administered by a certified practitioner alternating the colors (red, blue) of the exam for a given subject to avoid learning effects with repeated administration.

7. Be receiving donepezil (maximum dose: ≥10-mg, ≤15-mg) for symptomatic treatment of cognitive impairment associated with Alzheimer's dementia. The dose level must be stable for at least 1 month prior to screening.

8. Have a reliable and competent trial partner/caregiver who has a close relationship with the subject, has face-to-face contact at least three days a week for a minimum of six waking hours a week, and is willing to accompany the participant, if desired, to trial visits. Overnight stays at the clinic for the partner/caregiver are not required but may be requested at the discretion of investigator after consultation with the Sponsor. The trial partner/caregiver should understand the nature of the trial and adhere to trial requirements (eg, dosing, visit schedules, and nature and number of evaluations).

Demographics

9. Is male or female, from 50 years to 85 years of age inclusive, at the time of signing the informed consent.

Male Participants

Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

10. Male participants are eligible to participate if they agree to the following during the intervention period and for at least an additional 90 days (a spermatogenesis cycle) after the last dose of study intervention:

- Refrain from donating sperm

PLUS either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception unless confirmed to be azospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:

  - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

Female Participants

11. A female participant is eligible to participate if:

    - She is a WONCBP, as defined in Appendix [5].

Informed Consent

12. The participant (or legally acceptable representative if applicable) provides written informed consent for the study. The participant may also provide consent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

Additional Categories

13. Is willing to comply with the study restrictions (see Section 5.3 for a complete summary of study restrictions).

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. Is positive for hepatitis B surface antigen, hepatitis C antibodies or HIV.

2. Is at imminent risk of self-harm, based on clinical interview and responses on the C-SSRS, or of harm to others in the opinion of the investigator. Participants must be excluded if they report suicidal ideation with intent, with or without a plan or method (eg, positive response to item 4 or 5 in the assessment of suicidal ideation on the C-SSRS) in the past 5 years or suicidal behavior in their lifetime.

3. Had major surgery, donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the pretrial (screening) visit.

4. Has a history of clinically significant endocrine, gastrointestinal, cardiovascular, hematological, hepatic, immunological, renal, respiratory, genitourinary, or major neurological (including stroke and chronic seizures) abnormalities or diseases that are not under medical control over the past 2 months. Participants with a remote history of uncomplicated medical events (eg, uncomplicated kidney stones, as defined as spontaneous passage and no recurrence in the last 5 years, or childhood asthma) may be enrolled in the study at the discretion of the investigator.

5. Candidates should not have a history of asthma, COPD, urinary obstructions or GI bleeding.

6. Has a history of cancer (malignancy).

   Exceptions: (1) Adequately treated non-melanomatous skin carcinoma or carcinoma in situ of the cervix or; (2) Other malignancies which have been successfully treated with appropriate follow up and therefore unlikely to recur for the duration of the study, in the opinion of the investigator and with agreement of the Sponsor (eg, malignancies which have been successfully treated ≥10 years prior to the prestudy [screening] visit).

7. Participant has an estimated eGFR ≤60 mL/min/1.73 m^2 based on the MDRD.

MDRD Equation:

eGFR (mL/min/1.73 m^2) =
175 x (serum creat)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 [if female]) x (1.212 [if African American])

At the discretion of the investigator a measured creatinine clearance, as determined by a 24-hour urine collection, may be used in place of, or in conjunction with, the estimate of the eGFR.

Participants who have an eGFR or measured creatinine clearance of up to 10% below of either 80 mL/min (for creatinine clearance) or 80 mL/min/1.73m2 (for eGFR) may be enrolled in the study at the discretion of the investigator.

8. Has a history of significant multiple and/or severe allergies (eg, food, drug, latex allergy), or has had an anaphylactic reaction or significant intolerability (ie, systemic allergic reaction) to prescription or non-prescription drugs or food.

9. Has evidence of a clinically relevant or unstable psychiatric disorder, based on DSM-5 criteria, including schizophrenia or other psychotic disorder, bipolar disorder, or delirium at the time of the pre-study (screening) visit, or has a history of clinically significant psychiatric disorder of the last 5 years. Candidates may be excluded if they currently manifest Neuropsychiatric Symptoms of Dementia, specifically episodes of aggression, emotional outbursts or agitation. Following consultation between the Investigator and the Sponsor, a history of major depressive disorder, generalized anxiety disorder, and/or insomnia under good control for ≥ 2 months on stable medical therapy may not be exclusionary.

Prior/Concomitant Therapy

10. All medications being taken by candidates for enrollment in the study should be reviewed by the PI and the Sponsor to determine their propensity for altering MK-1942 exposure, or for MK-1942 to interfere with the metabolism of the medication. Medications prescribed for the candidate that are stably treating a condition should not be interrupted. Candidates should not be enrolled if they are taking [redacted] Enrollment of candidates taking prescription drugs that can alter QTi for an underlying condition (including: anti-arrhythmics

[quinidine, procainamide, disopromide, dofetilide, sotalol], some antihistamines, antidepressants [tricyclics, doxepin, fluoxetine] and antimicrobials) should be avoided. See Section 8.1.5 for more examples of excluded agents.

Prior/Concurrent Clinical Study Experience

11. Has participated in another investigational study within 4 weeks (or 5 half-lives, whichever is greater) prior to the prestudy (screening) visit. The window will be derived from the date of the last visit in the previous study.

Diagnostic Assessments

CCI [redacted]

13. Has a QTc interval ≥470 msec (for males) or ≥480 msec (for females).

Other Exclusions

14. Is under the age of legal consent.

15. Is a smoker and/or has used nicotine or nicotine-containing products (eg, nicotine patch and electronic cigarette) within 3 months of screening.

16. Consumes greater than 3 glasses of alcoholic beverages (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day. Participants who consume 4 glasses of alcoholic beverages per day may be enrolled at the discretion of the investigator.

17. Consumes excessive amounts, defined as greater than 6 servings (1 serving is approximately equivalent to 120 -mg of caffeine) of coffee, tea, cola, energy drinks, or other caffeinated beverages per day.

18. Is a regular user of cannabis, any illicit drugs or has a history of drug (including alcohol) abuse within approximately 2 years. Participants must have a negative UDS prior to randomization.

19. Presents any concern by the investigator regarding safe participation in the study or for any other reason the investigator considers the participant inappropriate for participation in the study.

20. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

5.3.1.1 Diet Restrictions

Fasting requirements for study procedures, including but not limited to laboratory safety evaluations, are specified below.

Participants will fast for at least 8 hours prior to laboratory safety evaluations.

On all dosing days, participants will fast from all food and drinks, except water, for at least 8 hours prior to study drug administration in the morning and for 2 hours post-dose following the morning and evening dose. After the 2-hour post-dose procedures have been completed, subsequent meals and snacks will be unrestricted in caloric content, composition and timing, except for dinner. Dinner must be consumed at least 2 hours prior to administration of the second dose of study treatment. Participants will fast from all food and drinks except water between meals and snacks. The caloric content and composition of meals will be the same on each day in each panel.

Water will be provided during study drug administration, with the restrictions noted above. Water will be restricted 1 hour prior to and 1 hour after study drug administration.

Each study drug administration will need to be taken with at least 240 mL (not to exceed 500 mL) of water.

5.3.1.2 Fruit Juice Restrictions

Participants will refrain from the consumption of grapefruit juice, grapefruits, and grapefruit products beginning approximately 2 weeks prior to administration of the initial dose of study drug, throughout the study including the washout interval between treatment periods and until the post-study visit.

On full PK sampling days, participants will refrain from the consumption of all fruit juices 8 hours prior to study drug administration and 2 hours following the morning and evening dose.

On intermediate days and all other days during the study, the consumption of all fruits and fruit juices (except for grapefruit, grapefruit juices, and grapefruit products) is allowed.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

Participants will refrain from consumption of caffeinated beverages or xanthine-containing products from 8 hours prior to the pre-study and post-study visits. On full PK sampling days participants will refrain from consumption of caffeinated beverages or xanthine-containing products from 8 hours prior to study drug administration in the morning, and for 2 hours

following the morning and evening dose. At all other times, caffeinated beverages or xanthine-containing products will be limited to no more than 6 units per day amounts (>6 units: 1 unit = 120-mg of caffeine).

5.3.2.2 Alcohol Restrictions

Participants will refrain from consumption of alcohol 24 hours prior to the pre-study and post-study visits and while domiciled on the CRU.

At all other times during the study (screening to post-study visit), alcohol consumption is limited to no more than approximately 3 alcoholic beverages or equivalent (1 glass is approximately equivalent to: beer [354 mL/12 ounces], wine [118 mL/4 ounces], or distilled spirits [29.5 mL/1 ounce]) per day.

5.3.2.3 Tobacco Restrictions

Smoking (and/or the use of nicotine/nicotine-containing products) is not permitted during the study.

5.3.3 Activity Restrictions

Participants will avoid unaccustomed strenuous physical activity (ie, weight lifting, running, bicycling, etc.) from the pre-study (screening) visit until administration of the initial dose of study drug, throughout the study (including washout intervals between treatment periods) and until the poststudy visit.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information may be included, as outlined in the eCRF entry guidelines. Minimal information may include demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements.

5.5 Participant Replacement Strategy

If a participant discontinues from study intervention OR withdraws from the study a replacement participant may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement participant will generally receive the same intervention or intervention sequence (as appropriate) as the participant being replaced. The replacement participant will be assigned a unique treatment/randomization number. The study site should contact the Sponsor for the replacement participant's treatment/randomization number.

The replacement participant may begin dosing at the subsequent dose level for that panel, based on investigator and Sponsor review and discussion.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies provided by the Sponsor will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 7.

Table 7 Study Interventions

Arm Name	Arm Type	Interven-tion Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen	Use	IMP/ NIMP	Sourcing
AD Patients	Experi-mental	MK-1942	Drug	Capsule	1-mg 5-mg 10-mg	All dosage levels *	Oral	BID dosing for up to 28 days	Experi-mental	IMP	Provided centrally by Sponsor
AD Patients	Experi-mental	Donepezil	Drug	Tablet	5-mg 10-mg	All dosage levels	Oral	QD dosing for up to 28 days	Thera-peutic	NIMP	Provided by participant
AD Patients	Placebo	Placebo to MK-1942	Placebo	Capsule	N/A	All dosage levels	Oral	BID dosing for up to 28 days	Experi-mental	IMP	Provided centrally by Sponsor

Definition Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.

* Doses of MK-1942 may be adjusted based on available safety/PK data from previous panels. The required dose will be achieved by administering multiples of the available capsule strength.

All supplies indicated in Table 7 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided inSection 4.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

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 study interventions in accordance with the protocol and any applicable laws and regulations.

If a patient elects to go home during the allotted period at each dose level, the investigator should take care to ensure that the study treatment for at-home dosing is packaged so that its temperature is maintained at 0-8 during transit.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Participants will be assigned randomly according to a computer-generated allocation schedule unique to each part of the study. Refer to Table 8.

Table 8 Sample Allocation Schedule

N	Dosing
n=18	8-mg MK-1942 BID x 7D; 15-mg MK-1942 BID x 7D; 30-mg MK-1942 BID x 7D; *≤50-mg MK-1942 BID x 7D* (*Provisional Dose Level*)
n=6	PBO to MK-1942 BID x 21 [28] D

6.3.2 Stratification

No stratification based on age, sex or other characteristics will be used in this study.

6.3.3 Blinding

A double-blinding technique will be used. MK-1942 and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified study site personnel. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

Donepezil administration will be conducted as open label; therefore, the Sponsor, investigator, and participant will know the intervention administered.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment plan require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

If a participant does not discontinue all prior medications within 14 days or 5 half-lives of the first dose of study intervention, he/she may be included in the study if the investigator can rationalize that the specific use of a prior medication is not clinically relevant within the context of the study.

Concurrent use of any prescription or nonprescription medication, or concurrent vaccination, during the ongoing study (ie, after randomization or intervention allocation) must first be discussed between the investigator and Sponsor prior to administration, unless appropriate medical care necessitates that therapy or vaccination should begin before the investigator and Sponsor can consult. The participant will be allowed to continue in the study if both the Sponsor and the investigator agree.

CCI [redacted]. Any prescribed medications used to stably treat a screening candidate or enrollee should be evaluated by the investigator in cooperation with the Sponsor to determine its propensity to interact with MK-1942 in any way before altering the treatment or enrolling the candidate. A more complete list of concomitant medications that should be avoided include:

1. Drugs that can alter QTi for an underlying condition (including: anti-arrhythmics [quinidine, procainamide, disopromide, dofetilide, sotalol], some antihistamines, and antimicrobials) should be avoided.

2. All AChEI's other than donepezil (physostigmine, neostigmine, echothiophate, pyridostigmine, rivastigmine, galantamine, tacrine, edrophonium, succinylcholine, etc.).

3. All medications with anticholinergic effects (atropine, darifenacin, dicyclomine, diphenoxylate with atropine, hydroxyzine, fesoterodine, glycopyrrolate, hydroxyzine, hyoscyamine, ipratropium, oxybutynin, promethazine, tolterodine, trospium, promethazine).

4. Sedatives/benzodiazepines (eg, alprazolam, diazepam). Use of some non-benzodiazepine medications for sleep may be acceptable if stable for at least two months before the Screening Visit, following review by the Investigator and Sponsor.

5. Narcotic analgesics (eg, codeine, morphine, hydromorphone, oxycodone).

6. Thyroid hormone replacement.

7. CCI [redacted]

8. Any herbal/natural product containing St John's wort, valerian, cassia, or licorice (glycyrrhizin) are restricted from use.

CCI

[redacted]

Paracetamol/acetaminophen may be used for minor ailments without prior consultation with the Sponsor.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

6.6 Dose Modification (Escalation/Titration/Other)

6.6.1 Stopping Rules

The following stopping rules will be employed during the conduct of this study.

Overall dose escalation will be limited by achievement of NOAEL exposure limits, loss of participants due to intolerance, or completion of the scheduled dose escalation.

Discontinuation of an individual participant from the study will be considered in the event of: clinically significant abnormalities in any safety tests as confirmed by the investigator; or any medical or non-medical circumstances which, in the opinion of the investigator, pose a risk to the patient by continuing in the study, or which do not allow the patient to adhere to protocol requirements. The Sponsor medical monitor should be notified within approximately 24 hours when either of these circumstances occurs.

The stopping rule listed below will be employed during the conduct of this study. If this criterion is met, the study may be paused until the Sponsor has reviewed the totality of data available.

a. An individual participant reports a Serious Adverse Event considered related to the study drug by the investigator. Two (2) or more participants within a Part (at the same dose level) report Severe Non-serious Adverse Events considered related to the study drug by the investigator.

If any of these criteria are met, subsequent doses of treatment for remaining participants may be adjusted (maintained at the same level, decreased or halted) based upon joint agreement of the Sponsor and investigator.

6.6.2 Dizziness/Nausea Stopping Criteria

<u>Dizziness</u>

Previous investigations (MK-1942-001, 002, 003) reported increases in the incidence and severity of dizziness episodes with doses of MK-1942 ≥8-mg. These results suggest that the AE of dizziness may occur over the dose range proposed for this study and that the number

and severity of dizziness episodes should be monitored as part of the dose escalation stopping criteria.

The following parameters are used for determining whether to adjust dosing for an individual based on the presence of dizziness:

A sustained symptom, defined as lasting ≥ 4 hours in duration and;

A severity of Grade 2 ("Moderate") intensity of dizziness, defined as including:

- Subject reports feeling a spinning or swaying movement that is not relieved when supine; AND
- Subject reports feeling unsteady or about to lose their balance upon walking (postural dizziness); AND/OR
- The Targeted Neurological Examination records that gait or extraocular movements are impaired.

If a participant reports sustained dizziness that, in the opinion of the investigator, is of moderate or greater severity and is related to study drug administration, then the dose for that participant will not be escalated. Continued dosing of the individual at the same or a lower level may be considered, or dosing may be stopped.

Nausea

Episodes of nausea were reported during studies MK-1942-001 (see MK-1942 IB) and MK-1942-002 [Sec. 2.2.3]. These events were observed less frequently than those of dizziness and were mild to moderate in intensity. The results suggest that the AE of nausea may occur over the dose range proposed for this study and that the number of episodes and their severity should be monitored as part of the dose escalation stopping criteria.

The definition of Grade 2 ("Moderate") severity nausea includes signs and symptoms that interfere with activities of daily living but require no treatment or intervention. If participants show sustained (> 4 hrs) physical signs and/or symptoms of nausea that, in the opinion of the investigator, are of moderate or greater severity and are related to study drug administration, then the dose for that participant will not be escalated. Continued dosing at the same or a lower level may be considered, or dosing for that individual may stop. If considered necessary by the investigator, supportive care may be provided until the signs/symptoms return to baseline.

Stopping Criteria

If >2 subjects meet the criteria defined above, there will be no dose escalation. Administration of study treatment to all participants may continue at the same or lower dose, for a longer duration of administration (not to exceed the 28-day limit), or may be halted, with agreement of the investigator and Sponsor.

These rules are not meant to be comprehensive but to provide clear guidance for the adjustment or discontinuation of dosing. However, due to the uncertain nature of Phase 1 trials, these rules should not be considered a substitute for clinical judgment. If unforeseen events demonstrate that participants meet these stopping criteria, but clinical judgment allows for continuance, then with the agreement of the Investigator and the Sponsor, and with the consent of the participant, dosing may be continued. Conversely, if the participant does not meet the criteria warranted by the stopping rules but clinical judgment mandates that dosing be halted, then dosing of the participants may be discontinued.

Participant Lost to Follow-up

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3., Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

6.7 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention allocation/randomization schedule for the study to unblind participants and to unmask study intervention identity . The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.10). The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period/vaccination regimen will still continue to participate in the study as specified in Section 1.3 and Section 8.1.9, or if available, a protocol clarification letter.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Sections 8.1.9.

A participant must be discontinued from study intervention but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant's treatment assignment has been unblinded by the investigator, MSD subsidiary, or through the emergency unblinding call center.
- The participant interrupts study intervention administration for more than 2 consecutive days or has 2 cumulative missed doses.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- The participant has a positive UDS at any time during the course of the study.

For participants who are discontinued from study intervention all applicable discontinuation activities will be performed according to Section 8.1.9, or if available, a protocol clarification letter.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Participants may withdraw from the study at any time for any reason. If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

A participant must be withdrawn from the study if:

- The participant or participant's legally acceptable representative withdraws consent from the study.
- Participant is lost to follow-up

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.9. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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

- Procedures conducted as part of a site generic screening (with an ERC/IRB approved site generic screening consent) on potential participants (eg, blood count, vital signs, ECG, etc.) and obtained before signing of study ICF may be utilized for screening or baseline purposes provided the procedures met the protocol specified criteria and were performed within the screening window defined in this protocol.

The maximum amount of blood collected from each participant over the duration of the study will not exceed 500 mL (Appendix 8).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study or future biomedical research.If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate consent is in place.

8.1.1.1 General Informed Consent

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

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

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

The participant or his/her legally acceptable representative will be asked to sign consent at the point of initial radiographic disease progression.

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the future biomedical research consent to the participant, answer all his/her questions, and obtain written informed consent before performing any procedure related to future biomedical research. A copy of the informed consent will be given to the participant.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

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[redacted]

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after

the participant provides written informed consent. At the time of intervention randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 4 weeks or 5 half-lives before the screening visit. Any medications necessary for keeping a candidate stably treated for an underlying condition should be reviewed by the PI for potential interference with/by the study medication [redacted] and brought to the attention of the Sponsor for mutual agreement on whether to enroll the candidate in the study (Section 6.5). Participants will be stably maintained on donepezil (≥10-mg, ≤15-mg) for at least 1 month prior to enrollment.

8.1.5.2 Concomitant Medications

Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study. Participants will be stably maintained on donepezil (≥10-mg, ≤15-mg) for at least 1 month prior to enrollment.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive an allocation number. The allocation number identifies the participant for all procedures occurring after treatment allocation. Once an allocation number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 allocation number.

8.1.8 Study Intervention Administration

Study intervention should begin on the day of treatment allocation/randomization or as close as possible to the date on which the participant is allocated/assigned. All doses of study treatment (MK-1942/placebo) will be provided as dry filled capsule and matching placebo.

These will be administered orally with at least 240 mL (not to exceed 500 mL) of water upon completion of all pre-dose procedures for that day, with administration of study medication witnessed by the investigator and/or study staff. Subjects will not be allowed access to food for 2 hours after both the morning and evening doses.

8.1.8.1 Timing of Dose Administration

The first oral doses of MK-1942/placebo will be administered in the morning at approximately the same time every day. After all pre-dose procedures are completed on the morning of Day 1, either MK-1942 or placebo will be administered (Section 8.1.8), with the time of administration constituting Time “0”. All capsules will be distributed and consumed within 10 minutes of the recorded administration time. Participants will remain resting in bed in a semi-recumbent position for approximately 2 hours after dosing. Participants may ambulate freely after the 2-hour VS and ECGs if no clinically significant changes are observed.

Participants will receive the second daily oral dose of MK-1942/placebo approximately 12 hours after the time the first daily dose was administered. All capsules will be administered within 10 minutes of the of the exact time when treatment is administered, and that administration time recorded. On Day 21 (28), only the morning dose will be administered. Participants will remain resting in bed in a semi-recumbent position for approximately 2 hours after dosing. Participants may ambulate freely after the 2-hour VS and ECG measures if no clinically significant changes are observed.

Donepezil will be administered in the mornings at approximately the same time as MK-1942/placebo. If participants do not usually take their Donepezil in the mornings, they should be instructed to start taking it in the morning starting on Day -7.

8.1.9 Discontinuation and Withdrawal

The investigator or study coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the study. If a participant discontinues for any reason at any time during the course of the study, the participant may be asked to return to the clinic (or be contacted) for a poststudy visit as per the number of days described in Section 8.10.4) to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety follow-up time frame as specified in Section 8.4.1, the investigator should perform a follow-up telephone call at the end of the follow-up period (Section 8.4.1) to confirm if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's consent for future biomedical research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant’s personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.10 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant’s intervention assignment, the investigator who is qualified physician should make reasonable attempts to enter the intensity grade of the AEs observed, the relation to study drug, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

If unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.

Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants whose treatment assignment has been unblinded by the investigator or medically qualified designee and/or nonstudy treating physician must be discontinued from study intervention but should continue to be monitored in the study.

8.1.11 Domiciling

Participants will report to the clinical research unit (CRU) on Day -2 prior to the scheduled day of administration of the study treatment or at the discretion of the investigator.

Participants may be domiciled in the unit for -2 days before dosing study drug, for up to 28 days of treatment, and with an additional three days of in-house, post-treatment follow up. Participants will be released from the CRU with instructions to return for the post-study examination, to be performed 14 days after the last day of dosing.

At the discretion of the investigator, participants may request to go home for days 5 and 6 of each dose level. At-home monitoring of AEs and treatment compliance will be conducted by daily telephone calls from the CRU. Participants should return to the CRU the evening of day 6 of each dose level in order to be ready for procedures conducted the following morning.

At the discretion of the investigator, participants may be requested to remain overnight in the CRU for longer than 30 days. Participants may be permitted to leave the unit for emergency situations only during the domiciling period at the discretion of the investigator after discussion with the Sponsor. The decision on how to continue monitoring the participant will be at the discretion of the investigator after discussion with the Sponsor.

8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy/Immunogenicity Assessments

There are no direct efficacy assessments in this study.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood to be drawn over the course of the study (from pre-study to post-study visits), including approximate blood volumes drawn by visit and by sample type per participant, can be found in Appendix 8.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. Height and weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Body Mass Index (BMI)

Body Mass Index equals a person's weight in kilograms divided by height in meters squared (BMI=kg/m^2). Body Mass Index will be rounded to the nearest whole number according to the standard convention of 0.1-0.4 round down and 0.5-0.9 round up.

Body weight and height will be obtained with the participant's shoes off and jacket or coat removed.

8.3.2 Vital Signs

- Oral, tympanic, or temporal body temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in the semi-recumbent and/or standing position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 10 minutes of rest by the participant in a quiet setting without distractions.

8.3.2.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

Participants should be resting in a semi-recumbent position for at least 10 minutes prior to having VS measurements obtained. Semi-recumbent VS will include HR and BP. The correct size of the BP cuff and the correct positioning on the participants' arm is essential to increase the accuracy of BP measurements.

The pre-dose (baseline) HR and BP will be triplicate measurements, obtained at least 1-2 minutes apart within 3 hours before dosing MK-1942 on Day 1. The mean of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). On all other days indicated in the SoA (See Section 1.3) pre-dose HR and BP will be single measurements. Post-dose VS measurements will be single measurements unless there is an out-of-range reading. In this case, at least three measures of VS (either resting or orthostatic HR, BP) will be taken within a 15-minute period, or until readings fall into normal range.

Participants will continue to rest semi-recumbent from dosing until 2 hours post-dose, except to stand for the measurement of orthostatic VS or other study-related procedures.

Body Temperature

Body temperature will be measured. The same method must be used for all measurements for each individual participant and should be the same for all participants.

8.3.2.2 Orthostatic Vital Signs

Orthostatic VS (HR and BP) will be obtained. Participants should be semi-recumbent for at least 10 minutes and then stand upright for 2 minutes prior to measurement of orthostatic VS.

8.3.3 Electrocardiograms

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry prior to lead placement. Participants may need to be shaved to ensure proper lead placement. Female participants may need to remove interfering garments.

Participants should be resting in the semi-recumbent for at least 10 minutes prior to each ECG measurement.

The correction formula to be used for QTc is Fridericia.

As repeat ECGs are required in this study, the clinical site will decide whether to leave the electrodes in place or mark the position of the electrodes for subsequent ECGs. To mark the position of the electrodes, 12-lead electrode sites will be marked on the skin of each participant with an ECG skin marker pen to ensure reproducible electrode placement.

All ECGs will be taken in triplicate at least 1-2 minutes apart at the times/dates indicated in the SoA (See Section 1.3). The mean of these measurements will be used to calculate the change from baseline for safety evaluations and for rechecks, if needed. Pre-dose ECGs will be obtained within 3 hours before dosing MK-1942/placebo.

During each treatment period, if a participant demonstrates an increase in mean QTc interval

≥ 60 msec compared to the mean pre-dose baseline measurement, the participant will be monitored by recording 12-lead ECGs in triplicate every 15 minutes for at least 1 hour, or until the QTc is within 60 msec of baseline. If prolongation of the QTc interval ≥60 msec persists, a consultation with a study cardiologist may be appropriate and the Sponsor should be notified.

If the QTc interval is ≥500 msec, the Sponsor should be notified, and the ECGs should be reviewed by a cardiologist. The ECG reader will be blinded to treatment, treatment period and timepoint. The participant may be telemetry-monitored until the QTc is < 500 msec or should be considered for transfer to a location where closer monitoring and definitive care (eg, a cardiac or intensive care unit) is available.

If the participant has unstable hemodynamics or if any clinically significant dysrhythmias are noted, the participant should be immediately transferred to an acute care setting for definitive therapy.

A study cardiologist will be consulted by the PI as needed to review ECG tracings with abnormalities.

8.3.4 Neurological Exams

The full neurological exam monitors aspects of mental status, cranial nerve function, motor system function, reflexes, coordination and gait and sensory function (Appendix 11) and will be administered at screening and the post-trial exam. The targeted neurological exam contains Modules 1, 2 and 5 of the general examination, focusing on arousal, cranial nerve function, and gait.

8.3.5 Mini-Mental State Examination (MMSE-2)

The MMSE-2 will be administered to the participant in paper form, scored and recorded by the principal investigator or trained designee according to the instructions in the operations manual.

8.3.6 WAIS-R Digit Symbol Substitution Test (DSST)

The DSST will be administered to the participant in paper form and scored and recorded by the principal investigator or trained designee according to the instructions in the operations manual.

8.3.7 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.8 Suicidal Ideation and Behavior Monitoring

8.3.8.1 Clinical Assessments for Suicidal Ideation and Behavior Monitoring

Suicidal ideation and behavior will be prospectively assessed during this study using the C-SSRS. The C-SSRS should be administered by trained raters at the time points indicated in the SoA. In addition, C-SSRS will be administered at any unscheduled visit where safety assessments are performed. The C-SSRS will not be routinely administered at visits with a sole purpose of PK sampling and/or witnessed study intervention administration. Site staff should review the contents of the C-SSRS for completeness. If the C-SSRS is administered by someone other than the investigator, consider providing the completed C-SSRS to the investigator for review, prior to their assessment of the participant and to further inform their evaluation. The C-SSRS is not explicit about whether the participant specifically has ideation at the time of screening. If a participant reports a prior history of ideation/behavior at screening, the assessor should also inquire and document if this is also present at the time of the screening visit.

Participants who at any time during this study report suicidal ideation or behavior that is considered an AE, either between visits or during visit interviews, must be assessed by the investigator. Participants 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 mental health nurse practitioner (or comparable professional qualification in countries outside the United States). Only participants 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 study may continue in the study; other participants must be discontinued from study participation and receive appropriate clinical follow-up care to ensure their safety. In addition, all AEs of suicidal ideation or behavior must be recorded as an ECI (See Section 8.4.7). Sites are to designate 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.

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before intervention allocation/randomization, must be reported by the investigator for randomized participants only if the event 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.

From the time of intervention allocation/randomization through 14 days following cessation of intervention, all AEs, SAEs and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 9.

Table 9 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
Nonserious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 24 hours of learning of event

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AE and/or SAE and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

This section is not applicable.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Disease related events and or disease related outcomes not qualifying as AEs or SAEs are not applicable to this study.

8.4.7 Events of Clinical Interest

Selected nonserious and SAEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5.

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

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that must trigger an additional evaluation for an underlying etiology. The study site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

   It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this study.

3. Suicidal ideation and/or suicidal behavior. A supplemental document will be provided that contains guidance for additional information to be collected and reported for these events (Appendix 12).

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose of any drug administered as part of the trial exceeding the dose prescribed by the protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

8.6 Pharmacokinetics

The decision as to which plasma samples collected will be assayed for evaluation of PK/PD will be collaboratively determined by the Sponsor (eg, samples at lower doses may not be assayed if samples at higher doses reveal undetectable drug concentrations). If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

8.6.1 Blood Collection for Plasma MK-1942

Sample collection, storage, and shipment instructions for plasma samples will be provided in the operations manual.

8.7 Pharmacodynamics

PD parameters will not be evaluated in this study.

8.8 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all participants as specified in the SoA:

- Blood for Genetic Analysis.

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the participant signs the future biomedical research consent. If the planned genetic analysis is not approved, but future biomedical research is approved and consent is given, this sample will be collected for the purpose of future biomedical research.

Sample collection, storage, and shipment instruction for planned genetic analysis samples will be provided in the operations/laboratory manual.

8.9 Future Biomedical Research Sample Collection

If the participant signs the future biomedical research consent, the following specimens will be obtained as part of future biomedical research:

- Leftover main study plasma from MK-1942 assay will be stored for future research
- Leftover DNA for future research

8.10 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.10.1 Screening

Within approximately 5 weeks prior to intervention allocation/randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

Participants may be rescreened after consultation with the Sponsor. Rescreening should be conducted if more than 35 days have elapsed between the participant's initial screening and

planned randomization. Rescreening should include all screening procedures listed in the SoA, including consent review. CCI [redacted] Rescreen procedures cannot be conducted the day prior to intervention allocation/randomization if there are Day -1 procedures planned per protocol.

8.10.2 Treatment Period Visit

Refer to the SoA (Section 1.3) and Administrative and General Procedures (Section 8.1).

8.10.3 Discontinued Participants Continuing to be Monitored in the Study

At any point if a participant discontinues from treatment but continues to be monitored in the study, all of study procedures specified in the SoA may be completed at the discretion of the investigator and with Sponsor agreement. The subset of study procedures completed will be communicated in a PCL.

8.10.4 Poststudy

Participants will be required to return to clinic approximately 14 days after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs less than 14 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 14 days post the last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit.

8.10.5 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, taking the blood sample for MK-1942 is the critical procedure.

At any post-dose time point, the blood sample for MK-1942 needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Study procedures can be performed prior or after the prescribed/scheduled time.

The order of priority can be changed during the study with joint agreement of the investigator and the Sponsor Clinical Director.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

The following variance in procedure collection times will be permitted.

- PK Collection, as outlined in Table 10.

Table 10 Pharmacokinetic Sample (Blood) Collection Windows

PK Collection	PK Collection Window
0 - <1 hr	5 min
1 - <24 hr	15 min
24 - <48 hr	1 hr
48 - 72 hr	2 hr

- Predose standard safety evaluations:
  - Vital signs within 3 hrs prior to dosing
  - ECGs within 1 hour prior to dosing
  - Laboratory safety tests and physical exam within 24 hrs prior to dosing
- Postdose standard safety evaluations: vital signs, laboratory safety tests, targeted neurological exam, physical exam, and C-SSRS
  a. <24 hr postdose: may be obtained within 30 minutes before and 1 hr after the stated monitoring time.
  b. 24 hr - <48 hr postdose: may be obtained within 4 hr of the stated monitoring time.
- Post-dose ECG evaluations
  - <24 hours post-dose: should be taken within 15 minutes of stated recording time.
  - 24 hours post-dose: should be taken within 1 hour of stated recording time.
- Study drug administration: ± 30 mins of stated administration period (AM, PM) and ± 30 minutes of previous day's administration times for a given participant.

8.10.6 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

This is a Phase 1 assessment of MK-1942 in humans, and the PK, PD, and safety profiles of the compound is still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants.

As such, some alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data, but the maximum daily dose may not exceed those currently outlined in the protocol.

- Repeat of or decrease in the dose of the study intervention administered in any given period/panel
- Interchange of doses between panels
  - Entire period(s) or panel(s) may be omitted
  - Decrease in the duration (eg, number of days) of study intervention administration
  - Adjustment of the dosing interval (eg, divided doses [BID to QD, QD to BID, or vice versa])
  - Instructions to take study intervention with or without food or drink may also be modified based on newly available data
  - Modification of the PK sample processing and shipping details based on newly available data

The PK sampling scheme currently outlined in the protocol may be modified during the study based on newly available PK data (eg, to obtain data closer to the time of peak plasma concentrations). If indicated, these collected samples may also be assayed in an exploratory manner for metabolites.

Up to additional 50 mL of blood may be drawn for safety and/or PK analyses. The total blood volume withdrawn from any single participant will not exceed the maximum allowable volume during his/her participation in the entire study (Section 8).

The timing of procedures for assessment of safety procedures (eg, VS, ECG, safety laboratory tests, etc.) may be modified during the study based on newly available data. Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information. These changes will not increase the number of study procedures for a given participant during his/her participation in the entire study.

It is understood that the current study may employ some or none of the alterations described above. Any alteration made to this protocol to meet the study objectives must be detailed by the Sponsor in a letter to the Study file and forwarded to the investigator for retention. The letter may be forwarded to the IRB/IEC at the discretion of the investigator.

9 STATISTICAL ANALYSIS PLAN

This section contains a summary of the statistical analyses for this trial. Full detail is in the Statistical Methods (Section 9.6).

9.1 Statistical Analysis Plan Summary

Safety

Summary statistics and plots will be generated for raw laboratory safety tests, ECGs, and/or vital signs as well as for change from baseline, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline).

Frequency and severity of subjective reports of AEs over the dosing period will be closely monitored and reported. The counts and frequency of AEs will be summarized by treatment. In addition, posterior probabilities (PP) of the incidence of dizziness, nausea, emesis after co-administration of MK-1942 and donepezil to AD patients that are less than a target rate will be provided. Such analyses may also be provided for other AEs identified during the study. The target rate is determined from the incidence of an AE associated with MK-1942 alone from MK-1942 P004, and the maximum tolerable increase in the incidence of an AE. For example, if the true AE rate of MK-1942 alone is 40% and the maximum tolerable increase in AE incidence associated with MK-1942 + donepezil compared to MK-1942 alone is 20%, the target rate would be 60%. A posterior probability greater than 60% will be considered as tolerable.

Responses to the C-SSRS will be tabulated and the individual score > 0 will be listed. The difference from pre-treatment baseline values will also be determined.

Pharmacokinetics

Model-based PK Summary

Evaluation of the effects of donepezil on the PK of MK-1942 in AD patients

At each dose level, individual values of the plasma Cmax of MK-1942 on the last day of a titrated treatment regimen after co-administration of MK-1942 with donepezil to AD patients, as well as the Cmax of MK-1942 after administration of MK-1942 alone to HEV in MK-1942-004 will be natural log transformed and analyzed in an ANOVA model. The model contains one factor for treatment (MK-1942 alone in HEV, MK-1942+donepezil in AD patients).

Ninety percent (90%) CIs will be constructed for GMRs (MK-1942 + donepezil in AD patients/ MK-1942 alone in HEV) from the model after back-transformation. The hypothesis that the plasma Cmax of MK-1942 determined on the last day of a titrated treatment regimen (Day 21 [28]) when co-administered with donepezil to AD patients is similar to the Cmax obtained following administration of MK-1942 alone to HEV (MK-1942-004) will be supported if the 90% CI for the true GMR (MK-1942 + donepezil in AD / MK-1942 alone in HEV) is contained within the interval (0.5, 2.0). Ninety-five percent (95%) CIs for the least squares means by treatment will be constructed on the natural log scale and will reference a t-distribution. Exponentiating the least square means and the lower and upper limits of these

confidence intervals will yield estimates for the population geometric means and confidence intervals about the geometric means on the original scale. Similar analyses will be conducted with MK-1942 AUC0-12 and Ctrough.

Evaluation of the effects of MK-1942 on the PK of donepezil in AD patients

Separately for each PK parameter, individual AUC0-24 and Cmax of donepezil after co-administration of MK-1942 and donepezil, or donepezil alone (Day -1) will be natural log transformed and analyzed in linear mixed effect model. The model contains fixed effect for treatment (MK-1942 and donepezil, donepezil alone) and random effect for subject. Ninety-five percent (95%) CIs for the least squares means by treatment will be constructed on the natural log scale and will reference a t-distribution. Ninety percent (90%) CIs will be constructed for the true GMRs (MK-1942 + donepezil / donepezil alone) from the model after back-transformation.

Power

PK:

The estimated pooled, between-subject standard deviations on a log scale for MK-1942 Cmax on the last day of dosing following administration of 3-mg to 20-mg BID doses of MK-1942 for 5 to 10 days to healthy adults in MK-1942-002 is 0.225. Assuming the standard deviation is 30% higher in AD patients than HEV (ie, the between-subject standard deviation on a log scale for Cmax is 0.29 in AD patients), if the true GMR (MK-1942+donepezil in AD patients/MK-1942 alone in HEV) is 1.00, with 18 AD patients receiving MK-1942 and donepezil and 6 HEV receiving MK-1942 alone in MK-1942-004, there is a 99% probability that the 90% CI of the GMR will fall within the interval of (0.5, 2.0).

Safety:

With 18 AD patients receiving MK-1942 + donepezil and a target rate of 80%, if the true AE rate following administration of MK-1942 + donepezil in AD patients is 60%, there is a probability of 97% that co-administration of MK-1942 with donepezil is considered safe and tolerable.

9.2 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of, the Early Clinical Development Statistics Department in collaboration with the Quantitative Pharmacology and Pharmacometrics Department and Translational Pharmacology Department of the Sponsor.

If changes are made to the statistical analysis plan as outline below after the study has begun, these deviations to the plan will be listed, along with an explanation as to why they occurred, in the Clinical Study Report.

9.3 Hypotheses/Estimation

Hypotheses

- The plasma Cmax of MK-1942 determined on the last day of a titrated treatment regimen (Day 21 [28]) when co-administered with donepezil to AD patients is similar to the Cmax obtained following administration of MK-1942 alone to HEV in MK-1942-004. That is, the true GMR (MK-1942 + donepezil in AD / MK-1942 alone in HEV) is contained within the interval (0.5, 2.0).

Estimations

- The GMRs of plasma PK parameters (AUC0-24 and Cmax) for those treated with MK-1942+ donepezil versus donepezil alone in AD patients will be estimated.

9.4 Analysis Endpoints

Primary Endpoints

1. Safety: AEs, vital signs, electrocardiograms, clinical chemistry, hematology, urinalysis, targeted neurological exams, Columbia suicide severity rating scale.

   Baseline is defined as the pre-dose measurement at Day 1.

Secondary Endpoints

1. Pharmacokinetics: the plasma PK parameters of MK-1942 after administration of MK-1942 + donepezil - Cmax, Tmax, Ctrough, AUC0-12, AUC0-24 (days 21 and 28), and CLss/F (days 21 and 28), Vzss/F (days 21 and 28), apparent terminal t1/2 (Day last – 21 or 28 only).

2. Pharmacokinetics: the plasma PK parameters of donepezil after administration of donepezil alone and donepezil + MK-1942 (Days -1, 21, and 28) - Cmax, Tmax, and AUC0-24.

Exploratory Endpoints:

1. MMSE-2 and DSST scores obtained at baseline (screening) and from the last day of dosing.

2. 12-lead ECG parameters

9.5 Analysis Populations

The following populations are defined for the analysis and reporting of data. All participants will be reported, and their data analyzed, according to the treatment(s) they actually received.

All Subjects as Treated (ASasT): The All Subjects as Treated Population consists of all participants who received at least one dose of treatment. This population will be used for assessments of safety and tolerability.

Per-Protocol (PP): The Per-Protocol Population consists of the set of data generated by the subset of participants who comply with the protocol sufficiently to ensure that these data will be likely to exhibit the effects of treatment, according to the underlying scientific model.

Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations. Important protocol deviations will be identified to the extent possible prior to unblinding by individuals responsible for data collection/compliance, and its analysis and interpretation. Any participants or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all participants who are compliant with the study procedure as aforementioned and have available data from at least one dose level will be included in the Per-Protocol dataset. This population will be used for the PK analyses.

9.6 Statistical Methods

9.6.1 Safety

Summary statistics and plots will be generated for raw laboratory safety tests, ECGs, and/or vital signs as well as for change from baseline, as deemed clinically appropriate. Depending on the safety parameter, the difference from baseline will either be computed on the original scale (raw change from baseline) or on the log scale and back-transformed for reporting (percent change from baseline).

The frequency and severity of subjective reports of AEs over the dosing period will be closely monitored and reported. The counts and frequency of AEs will be summarized by treatment. In addition, posterior probabilities (PP) of the incidence of dizziness, nausea, emesis after co-administration of MK-1942 and donepezil to AD patients that are less than a target rate will be provided. Such analyses may also be provided for other AEs identified during the study. The target rate is determined from the incidence of an AE associated with MK-1942 alone from MK-1942 P004, and the maximum tolerable increase in the incidence of an AE. For example, if the true AE rate of MK-1942 alone is 40% and the maximum tolerable increase in AE incidence associated with MK-1942 + donepezil compared to MK-1942 alone is 20%, the target rate would be 60%. A posterior probability greater than 60% will be considered as tolerable.

Responses to the C-SSRS will be tabulated and the individual score > 0 will be listed. The difference from pre-treatment baseline values will also be determined.

9.6.2 Pharmacokinetics

Model-based PK Summary

Evaluation of the effects of donepezil on the PK of MK-1942 in AD patients

At each dose level, individual values of the plasma Cmax of MK-1942 on the last day of a titrated treatment regimen after co-administration with donepezil to AD patients, as well as the Cmax of MK-1942 after administration of MK-1942 alone to HEV in MK-1942-004 will

be natural log transformed and analyzed in an ANOVA model. The model contains one factor for treatment (MK-1942 alone in HEV, MK-1942+donepezil in AD patients).

Ninety percent (90%) CIs will be constructed for GMRs (MK-1942 + donepezil in AD patients/ MK-1942 alone in HEV) from the model after back-transformation. The hypothesis that the plasma Cmax of MK-1942 determined on the last day of a titrated treatment regimen (Day 21 [28]) when co-administered with donepezil to AD patients is similar to the Cmax obtained following administration of MK-1942 alone to HEV (MK-1942-004) will be supported if the 90% CI for the true GMR (MK-1942 + donepezil in AD / MK-1942 alone in HEV) is contained within the interval (0.5, 2.0). Ninety-five percent (95%) CIs for the least squares means by treatment will be constructed on the natural log scale and will reference a t-distribution. Exponentiating the least square means and the lower and upper limits of these confidence intervals will yield estimates for the population geometric means and confidence intervals about the geometric means on the original scale. Similar analyses will be conducted with MK-1942 AUC0-12 and Ctrough.

Evaluation of the effects of MK-1942 on the PK of donepezil in AD patients

Separately for each PK parameter, individual AUC0-24 and Cmax of donepezil when co-administered with MK-1942 or alone (Day -1) will be natural log transformed and analyzed in a linear mixed effects model. The model contains fixed effect for treatment (MK-1942 and donepezil, donepezil alone) and random effect for subject. Ninety-five percent (95%) CIs for the least squares means by treatment will be constructed on the natural log scale and will reference a t-distribution. Ninety percent (90%) CIs will be constructed for the true GMRs (MK-1942 + donepezil / donepezil alone) from the model after back-transformation.

Descriptive Statistics

Individual values will be listed for each PK parameter by dose level, and the following (non-model-based) descriptive statistics will be provided, if appropriate: N (number of participants with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log-scale).

Exploratory Analysis

MMSE-2 scores

In order to evaluate the change in cognitive function of AD patients, descriptive summary statistics of the values and the change from baseline values will provided for the MMSE-2 scores obtained at baseline (screening) and from the last day of dosing.

WAIS-R DSST scores

In order to evaluate the change in cognitive function of AD patients, descriptive summary statistics of the values and the change from baseline values will provided for the DSST scores obtained at baseline (Day -1), Day 14, and from the last day of dosing (Day 21 [28])

Concentration-QTc

The average of the triplicate measurements at any time point will be calculated prior to any further analysis. Fridericia's correction to QT ($QTcF = QT / RR^{1/3}$) will be made in order to correct for heart rate. The appropriateness of the correction factor (ie, 1/3) will be assessed via a linear mixed effects model with QTcF as the response variable and RR interval as a covariate and subject as a random effect, using data from the placebo treatment and the predose measurements of the active treatments. A slope estimate close to zero would indicate that Fridericia's correction provides an adequate correction to the original QT data; otherwise, an appropriate transformation on RR will be further explored.

The predose value on Day 1 will serve as baseline for calculating individual change from baseline at each time point. Observed plasma concentrations and observed QTcF change from baseline will be used to investigate the relationship between QTcF and plasma MK-1942 concentrations (placebo data will also be used in this assessment, with the plasma concentration of MK-1942 set to 0). Scatter plots of QTcF change from baseline versus corresponding time-matched MK-1942 concentration will be provided.

The QTcF change from baseline will be further evaluated using a linear mixed effects model with fixed effects for treatment (MK-1942, placebo), time point, continuous effects for QTcF baseline, plasma concentration. A double compound symmetry covariance structure will be assumed. The highest 'safe' drug concentration (C_safe), defined as the highest drug concentration whose upper limit of the two-sided 90% confidence interval (equivalent to a one-sided upper 95% confidence limit) of ΔΔQTcF (placebo- baseline- adjusted) less than 10 milliseconds (ms), will be reported. An estimate of the expected mean effect and 90% confidence interval of ΔΔQTcF will also be computed at the observed geometric mean Cmax for each MK-1942 dose of interest.

Additional modeling of the concentration and QTc data from this study may be conducted later as part of a broader evaluation of MK-1942's QTc prolongation potential. In that case, a separate Modeling Analysis Plan will be written prior to analysis.

9.6.3 General

For all analyses, data will be examined for departures from the assumptions of the statistical model(s) as appropriate; eg, heteroscedasticity, non-normality of the error terms.

Distribution-free methods may be used if a serious departure from the assumptions of the models(s) is observed, or suitable data transformations may be applied.

9.7 Interim Analyses

No interim analysis is scheduled.

9.8 Multiplicity

Since there is no primary hypothesis, no adjustments for multiplicity are needed.

9.9 Sample Size and Power Calculations

PK:

The estimated pooled, between-subject standard deviations on log scale for MK-1942 Cmax on the last day of dosing following administration of [redacted] BID doses of MK-1942 for 5 to 10 days in healthy subjects in MK-1942-002 is 0.225. Assuming the standard deviation is 30% higher in AD patients than HEV, i.e. the between-subject standard deviation on a log scale for Cmax is 0.29 in AD patients, if the true GMR (MK-1942+donepezil in AD patients/MK-1942 alone in HEV) is 1.00, with 18 AD patients receiving MK-1942 and donepezil and 6 HEV receiving MK-1942 alone in MK-1942-004, there is 99% probability that the 90% CI of the GMR will fall completely within the interval of (0.5, 2.0).

Safety:

With 18 AD patients receiving MK-1942 + donepezil and a target rate of 80%, if the true AE rate following administration of MK-1942 + donepezil in AD patients is 60%, there is a probability of 97% that the coadministration of MK-1942 and donepezil is considered safe and tolerable (Table 11).

Table 11 Operating Characteristics for a One AE Incidence Rate

Number of Subjects Receiving MK-1942 + Donepezil	**True Rate**	**Target Rate**	**Operating Characteristics "Go" means tolerable "Go" if PP (AE rate ≤ Target rate)> 60%**	
			Probability of "Go"	**Probability of "No Go"**
18	90%	80%	10%	90%
	80%	80%	51%	49%
	70%	80%	83%	17%
	60%	80%	97%	3%
18	70%	60%	14%	86%
	60%	60%	44%	56%
	50%	**60%**	**77%**	**24%**
	40%	60%	95%	5%

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud,

scientific/research misconduct or serious GCP-non-compliance is suspected, the issues are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). 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. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants 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.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

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

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

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

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with

standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.6 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

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

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

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

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

10.1.7 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

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

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during

the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 12 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 12 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose [nonfasting]	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone (as needed in women of nonchildbearing potential only) • [Serum or urine] [alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) if applicable] • [Serology [(HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)] [if applicable]			
NOTES: NOTES: • Urea is acceptable if BUN is not available as per institutional standard. • WBC Differential: Consider if results providing the absolute or % value will be acceptable or if absolute values are required. • Creatinine: GFR (measured or calculated) or creatinine clearance can be used in place of creatinine.				

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

- **Results in death**
- **Is life-threatening**
  - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- **Requires inpatient hospitalization or prolongation of existing 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 for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE.) A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.
- **Results in persistent or significant disability/incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

- **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer

- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:

  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).

  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).

  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE 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 product and the AE 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 AE:

- **Exposure:** Is there evidence that the participant 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 studies 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.

- **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 study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?

    - 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 study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND 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 PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention 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.

- 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:

    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

This section is not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.

  Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[b,c] • Intrauterine hormone-releasing systems (IUS)[c,d] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. b If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. c Male condoms must be used in addition to hormonal contraception. d IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this study as outlined in Section 8.9 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research.

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participant' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like gender, age, medical history and intervention outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the future biomedical research specimens 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 follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which

operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include: Lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. 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.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@merck.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618

2. International Council on Harmonization [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html

3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

This appendix is not applicable for this study.

10.8 Appendix 8: Approximate Blood Volume Table

Test	Pre-study	Treatment Periods	Post-study	Total Collections	mL Per Collection	Total mL/ Test
Laboratory Safety Tests	2	6	1	9	12.5	112.5
HIV/Hepatitis Screen	1			1	5	5
Blood for Planned Genetic Analysis	1			1	8.5	8.5
CCI						
Blood for plasma MK-1942		54		54	4	216
Blood for plasma donepezil		18		18	4	72
Total Blood Volume per Participant[a]						416.5 mL

[a] If additional pharmacokinetic, pharmacodynamic and/or safety analysis is necessary, additional blood (not to exceed 50 mL) may be obtained.

10.9 Appendix 9: 12-Lead Electrocardiogram Abnormality Criteria

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria	Potentially Significant Post-randomization Findings (clarification on action to take)
RHYTHM		
Sinus Tachycardia	>110 bpm	HR >110 bpm and HR increase of ≥25 bpm from baseline
Sinus Bradycardia	<40 bpm	HR <40 bpm and HR decrease of ≥5 bpm from baseline
Sinus Pause/Arrest	>2.0 seconds	>2.0 seconds
Atrial Premature Complex	> 1 beat	≥ 3 beats
Ventricular Premature Complex	All	≥ 3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR <40 bpm	Junctional Rhythm with HR <40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB With Left Anterior Hemiblock (LAHB)	New Onset LAHB
Right Axis Deviation	RBBB With Left Posterior Hemiblock (LPHB)	New Onset LPHB
CONDUCTION		
1st Degree AV Block	PR ≥230 ms	PR ≥ 230 ms + Increase of >15 ms; or PR Increase of >25%
2nd Degree AV Block	Mobitz Type II	Mobitz Type II
3rd Degree AV Block	All	All
LBBB	All	All
RBBB	RBBB With LAHB/LPHB as Defined Above	New Onset RBBB (Not Including Rate-related)
Incomplete Right BBB (ICRBBB) (QRS <120 ms)	No Exclusion	Nothing
Short PR/ Preexcitation Syndrome	Delta Wave + PR <120 ms	Delta Wave + PR <120 ms
Other Intra-Ventricular Conduction Delay	QRS ≥130 ms	QRS ≥130 ms + Increase of ≥10 ms
QTc (B or F)		
Male	QTc ≥470 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
Female	QTc ≥480 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
HYPERTROPHY		
Atrial Abnormalities	Definite Evidence of P Mitrale or P Pulmonale	Definite Evidence of P Mitrale or P Pulmonale

12-Lead Electrocardiogram Abnormality Criteria		
	Screen Failure Criteria	Potentially Significant Post-randomization Findings (clarification on action to take)
Ventricular Abnormalities	Voltage Criteria for LVH Plus Strain Pattern	Voltage Criteria for LVH Plus Strain Pattern
MYOCARDIAL INFARCTION		
Acute or Recent	All	All
Old	All	All
ST/T MORPHOLOGY		
ST Elevation Suggestive of Myocardial Injury	In 2 or more contiguous leads	In 2 or more contiguous leads
ST Depression Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions Suggestive of Myocardial Ischaemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Non-specific ST-T Changes (In 2 or More Leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER	All	All
Baseline is defined as Predose Day 1; ms=milliseconds, mm=millimeter		

10.10 Appendix 10: Algorithm for Assessing Out of Range Laboratory Values

For all laboratory values obtained at prestudy (screening) visit and/or predose evaluation:

A. If all protocol-specified laboratory values are normal, the participant may enter the study.

B. If a protocol specified laboratory value is outside of the parameter(s) outlined in the inclusion/exclusion criteria (including a repeat if performed), the participant will be excluded from the study.

C. If ≥1 protocol-specified laboratory value not specified in the inclusion/exclusion criteria is outside the normal range, the following choices are available:

    1. The participant may be excluded from the study;

    2. The participant may be included in the study if the abnormal value(s) is NCS (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).

    3. The participant may be included in the study if the abnormality is consistent with a pre-existing medical condition which is not excluded per protocol (eg, elevated eosinophil count in a participant with asthma or seasonal allergies), the medical condition should be annotated on the laboratory report.

    OR

    4. The abnormal test may be repeated (refer items a. and b. below for continuation of algorithm for repeated values).

    If the repeat test value is within the normal range, the participant may enter the study.

    If the repeat test value is still abnormal, the study investigator will evaluate the potential participant with a complete history and physical examination, looking especially for diseases that could result in the abnormal laboratory value in question. If such diseases can be ruled out, and if the abnormal laboratory value is not clinically relevant, then the participant may enter the study.

D. If there is any clinical uncertainty regarding the significance of an abnormal value, the participant will be excluded from the study

10.11 Appendix 11: The General and Targeted Neurological Exams

The General and Targeted Neurological Examination will be performed at the time points specified in the Schedule of Activities (Section 1.3).

Note to the investigator: **If at any time abnormalities are observed in the General or Targeted Neurological Exams, the Investigator should do additional examinations as needed based on his or her medical judgment.**

The General Neurological Examination

The General Neurological Examination includes all of the modules listed below and is intended to be a general screening examination.

MODULE 1 – MENTAL STATUS EXAMINATION

A. General Level of Arousal (generally assess general level of alertness, attentiveness, and concentration throughout the interview. Regarding attentiveness, note evidence of impaired attention or concentration. For example difficulty remembering or following instructions or distractibility may be signs of inattention)

B. Thought Processes and Language (generally assess logic, relevance, organization and coherence of volunteer's use of language throughout the interview).

C. Orientation (time, place, person).

D. Attention/Concentration

Ask the participant to count backwards from 100 by 7's ("Serial 7's") or ask to recite months backwards or spell a 5 unique letter word (eg "WORLD") backwards.

Note: To avoid learning effects, switch between tests throughout the study

E. Memory (test registration of 3 objects; then test immediate recall 5 minutes later).

Grade: **NORMAL or IMPAIRED and describe abnormality (for each, A to E, above). Normal performance on Serial 7's is getting to 65 with no more than one error.**

MODULE 2 – CRANIAL NERVE ASSESSMENT

A. II – Eyesight

B. II, III – Pupil Size and Reactivity

C. III, IV, VI – Extraocular Movements (range of motion, smooth pursuit, saccades, nystagmus).

1. Observe for nystagmus during eye movements, increased nystagmus at the end of gaze or other oculomotor changes (mild nystagmus at extremes of gaze is normal). Note direction of nystagmus

D. V – Facial Sensation, Jaw Strength

E. VII – Muscles of Facial Expression (wrinkle brow, squeeze eyes shut, smile)

F. VIII – Auditory Acuity (assessed using a bed-side screening test eg by rubbing fingers on each side of participant's head or by whispering numbers)

G. IX – Gag reflex

H. X – Swallow

I. XI – Shoulder shrug

J. Tongue Protrusion (midline)

Score: left and right (except for G, H, J)

Grade: **NORMAL or IMPAIRED and describe abnormality**

MODULE 3 - MOTOR SYSTEM

A. Muscle Tone

1. Ask the volunteer to relax.

2. Flex and extend the volunteer's elbows and knees (bilaterally).

3. There is a small, continuous resistance to passive movement.

4. Observe for involuntary movements (eg, tremor, tics, fasciculations). Observe for resistance to passive movement; observe for decreased (flaccid) or increased (rigid/spastic) tone.

Score: left and right

***Grade*: NORMAL, INCREASED or DECREASED**

B. Muscle Strength

1. Ask the participant to stand up from sitting without using hands

Grade: **NORMAL, IMPAIRED and describe abnormality**

2. Test proximal limb strength by having the volunteer flex and extend the knees and elbows against your resistance.

Test bilaterally and compare one side to the other.

Score: ***left and right***

Grade: **5/5: normal;**

4/5: movement against resistance impaired;

3/5: movement against gravity but not against resistance;

2/5: visible movement but not against gravity;

1/5: visible contraction;

0/5: no visible activity

3. Test distal limb strength by having the volunteer conduct dorsiflexion and plantar flexion of the volunteer's feet; finger abduction and handgrip strength against your resistance.

Test bilaterally and compare one side to the other.

Score: ***left and right***

Grade: **5/5: normal;**

4/5: movement against resistance impaired;

3/5: movement against gravity but not against resistance;

2/5: visible movement but not against gravity;

1/5: visible contraction;

0/5: no visible activity

C. Pronator Drift

1. Ask the volunteer to hold both arms straight forward with, palms up and eyes closed for ≈10-15 seconds as tolerated; watch for how well the arm position is maintained.

2. Instruct the volunteer to keep both arms still while you tap them briskly downward.

The volunteer should normally be able to maintain extension and supination. Inability to maintain extension and supination (and drift into pronation) indicates an upper motor neuron deficit.

***Score*: left and right**

***Grade*: NORMAL or IMPAIRED and describe abnormality**

MODULE 4 - REFLEXES

A. Biceps

B. Knee

***Note*: Other deep tendon reflexes may be tested at Investigator's discretion (eg elbow, wrist or Achilles tendon)**

***Score*: left and right**

***Grade*: NORMAL, INCREASED, DECREASED or ABSENT**

C. Babinski

***Score*: left and right**

***Grade*: NORMAL or ABNORMAL**

MODULE 5 - COORDINATION AND GAIT

A. Rapid, Rhythmic Alternating Movements

1. Testing each hand separately, ask the volunteer to tap the distal thumb with the tip of each finger, in sequence, as fast as possible.

***Score*: left and right**

***Grade*: NORMAL or IMPAIRED**

Reminder: If the rapid alternate movements are disturbed, the participant will be asked to strike his hand on the thigh, raise the hand, turn it over and then strike the back of the hand down on the same place. (This test is impaired in cerebellar disease, extra pyramidal disease and upper MN weakness.)

B. Point-to-Point Movements

1. Ask the volunteer to touch your index finger and their nose alternately several times. Move your finger about as the volunteer performs this task.

Score*: *left and right

***Grade*: NORMAL or IMPAIRED**

Reminder: If the point-to-point testing is disturbed, the participant will be asked to place one heel on the opposite knee and then run it down the shin to the big toe. Repeat this for both sides. (Impaired tests indicate cerebellar disease.)

C. Romberg

1. Ask the volunteer to stand with both feet together and eyes closed for 20 to 30 seconds without support.
2. Be prepared to catch the volunteer if they are unstable.

***Grade*: NORMAL or IMPAIRED**

D. Gait

1. Ask the volunteer to walk across the room, turn and come back (assess posture, balance, swinging of arms and movement of the legs).

***Grade*: NORMAL or IMPAIRED and describe abnormality**

2. Ask the volunteer to walk heel-to-toe in a straight line (tandem gait).

***Grade*: NORMAL or IMPAIRED and describe abnormality**

MODULE 6 - SENSORY

A. Light touch sense: cotton wisp on skin of forearms and legs, bilaterally.

B. Pin prick: safety pin touched lightly to skin of forearms and legs, bilaterally.

C. Vibration: tuning fork vibration detection in hands, feet bilaterally.

D. Stereognosis: (identify common objects placed in hand, eg, coin, key).

Score*: *left and right

***Grade*: NORMAL OR IMPAIRED and describe abnormality (for each A to F)**

The Targeted Neurological Examination

The Targeted Neurological Examination, which is intended to focus on tests where drug effects can be seen, includes the following tests only:

MODULE 1 – MENTAL STATUS EXAMINATION

A. General Level of Arousal (generally assess general level of alertness, attentiveness, and concentration throughout the interview. Regarding attentiveness, note evidence of impaired attention or concentration. For example difficulty remembering or following instructions or distractibility may be signs of inattention)

MODULE 2 – CRANIAL NERVE ASSESSMENT

B. II, III – Pupil Size and Reactivity

C. III, IV, VI – Extraocular Movements (range of motion, smooth pursuit, saccades, nystagmus

1. Observe for nystagmus during eye movements, increased nystagmus at the end of gaze or other oculomotor changes (mild nystagmus at extremes of gaze is normal). Note direction of nystagmus

MODULE 3 - MOTOR SYSTEM

B. Muscle Strength

1. Ask the participant to stand up from sitting without using hands

***Grade*: NORMAL, IMPAIRED and describe abnormality**

MODULE 5 - GAIT

B. Gait

1. Ask the volunteer to walk across the room, turn and come back (assess posture, balance, swinging of arms and movement of the legs).

***Grade*: NORMAL or IMPAIRED and describe abnormality**

2. Ask the volunteer to walk heel-to-toe in a straight line (tandem gait).

***Grade*: NORMAL or IMPAIRED and describe abnormality**

10.12 Appendix 12: Additional Information to be Collected from Subjects Who Report Suicidal Ideation and/or Behavior

Adverse events of suicidal ideation and/or behavior must be reported to Merck as an Event of Clinical Interest (ECI) within 24 hours of observation. Suicidal ideation and behavior may be identified through spontaneous participant reports and/or upon review of the C-SSRS responses or other assessment tools.

Participants who at any time during this study spontaneously report AEs of suicidal ideation or behavior, either as an outpatient or during visit interviews, or whose responses to the QIDS-SR16 (when assessed) or C-SSRS are suggestive of suicidal ideation and behavior, must be assessed by the investigator and referred for further mental health evaluation. Participants with treatment-emergent suicidal ideation and/ or 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 patients 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 study may continue in the study; others must be discontinued from study participation and receive appropriate clinical follow-up care to assure their safety.

The investigator will collect the following information, in addition to any other relevant information deemed appropriate by the investigator or Sponsor. It is important to also note pertinent negatives where applicable to convey that the information was collected. This information must be entered in INFORM in narrative format in the Adverse Experience free text fields. These data will be used to provide a narrative summary of the event.

10.13 Appendix 13: Abbreviations

Abbreviation	Expanded Term
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
AE	adverse event
ALT	Alanine aminotransferase
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
APaT	All-Participants-as-Treated
AST	Aspartate aminotransferase
ATD	accelerated titration design
AUC	area under the plasma concentration-time curve
β-hCG	β-human chorionic gonadotropin
BID	twice daily
BMI	body mass index
BP	blood pressure
BT	body temperature
CI	confidence interval
CG	Cockcroft-Gault
CNS	central nervous system
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
Cmax	maximum plasma concentration
CrCl	creatinine clearance
CRF	case report form
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
C-SSRS/SLA	C-SSRS since last assessment
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE 4.0	Common Terminology Criteria for Adverse Events, Version 4.0
Ctrough	trough plasma concentration
CCI [redacted]	
D	day
DBP	diastolic blood pressure
DFC	dry filled capsule
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic case report form
EDC	electronic data collection
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
F	fluoride
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle stimulating hormone
GCP	good clinical practice
GI	gastrointestinal
HBsAg	hepatitis B surface antigen

Abbreviation	Expanded Term
HBV	hepatitis B virus
HCl	hydrochloride
HEV	healthy elderly volunteer
HIV	human immunodeficiency virus
hr	hour
HR	heart rate
IB	Investigator's Brochure
ID/pbo	investigational drug/placebo
ICF	informed consent form
ICH	International Council on Harmonization
IEC	Institutional Ethics Committee
IMP/NIMP	Investigational/Non-Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
CCI [redacted]	
NCS	not clinically significant
NDA	New Drug Application
nH	Hill coefficient
NOAEL	no observed adverse effect level
Occ50	compound concentration resulting in 50% occupancy of a receptor
OSF	on-site formulation
PD	pharmacodynamic
PI	principal investigator
PK	pharmacokinetic
PO	orally
PP	per-protocol
QD	Quaque die (daily)
QTc	corrected QT interval
RNA	ribonucleic acid
RO	receptor occupancy
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
t1/2	half-life
tmax	time to maximum plasma concentration
UDS	urine drug screen
V	volume of distribution
VS	vital sign
WAIS	Wechsler adult intelligence scale
WBC	white blood cell
WONCBP	woman/women of non-childbearing potential

11 REFERENCES

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