Official Protocol Title:	A Clinical Study to Evaluate a Cognitive Platform to Support Development of Symptomatic Therapies in Participants at Risk for Alzheimer's Disease
NCT number:	NCT04730635
Document Date:	02-Dec-2022

Title Page

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Protocol Title: A Clinical Study to Evaluate a Cognitive Platform to Support Development of Symptomatic Therapies in Participants at Risk for Alzheimer's Disease

Protocol Number: 413-05

Compound Number: MK-0000

Sponsor Name:

Merck Sharp & Dohme LLC
(hereafter referred to as the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	137,207

Approval Date: 02 December 2022

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 05	02-DEC-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Amendment 04	30-SEP-2021	Modify inclusion criterion #2a by changing CDR Sum of Boxes score from "at least 3.5" to "at least 2.0" when the Global CDR is 0.5 for participants diagnosed with MCI.
Amendment 03	21-JUN-2021	Adjustments made to exclusion criteria to support enrollment.
Amendment 02	02-MAR-2021	Modify exclusion criterion #26 by shortening the exclusionary period for previous neuropsychological testing from 6 months to 4 weeks to support enrollment of participants who have been recently diagnosed with cognitive impairment or Alzheimer's disease.
Amendment 01	13-NOV-2020	Addition of ECG (and/or review of ECG report from 3 months prior) as a screening procedure to ensure enrollment of participants with no contraindication to donepezil
Original Protocol	30-SEP-2020	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 05

Overall Rationale for the Amendments:

Sponsor underwent an entity name change and update to the address.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Title Page Section 10.1.1 Code of Conduct for Clinical Trials	Sponsor entity name and address change	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
Section 5.2 Exclusion Criteria	Exclusion Criteria #6 – addition of "with Sponsor's approval" to the note: **Note:** Participants with a score of 5 or more who are not diagnosed with major depression following such an assessment may be included in the study with Sponsor's approval.	Clarification on when such participants may be included in the study

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion Criteria Section 10.10 Appendix 10: Abbreviations	Exclusion Criteria #11 – addition of the following exception: "Participants with a history of chronic hepatitis C infection with a documented cure and/or a positive serologic test for HCV with a negative HCV viral load may be included following Sponsor consultation." Addition of HCV to list of abbreviations	Exception added to support enrollment of participants diagnosed with AD who have been treated for hepatitis C with no active infection
Section 5.2 Exclusion Criteria	Exclusion Criteria #15 – Table 2 Prohibited Medications: For Analgesics/Narcotics, change the prohibited duration from "24-48 hrs" to "48 hrs" in the corresponding Notes column so that the exception now reads: "**Exception:** if dosing is ≤ 2 doses/week (i.e. not regularly used) this is acceptable. Prohibited 48 hrs before study visits.	Update made to remove ambiguity with respect to the duration when the medication is prohibited prior to study visits
Section 5.2 Exclusion Criteria	Exclusion Criteria #15 – Table 2 Prohibited Medications: addition of "Selected" to "Herbal Supplements/Vitamins" in the Prohibited Medications column and addition of "/vitamins" in the corresponding Notes columns to read "other herbal supplements/vitamins".	Clarification added noting that not all herbal supplements/vitamins are exclusionary and to contact Sponsor with questions on other herbal supplements/vitamins that are not listed

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion Criteria	Exclusion Criteria #26 – inclusion of the MMSE as an example: "Has undergone neuropsychological testing (including the MMSE) or cognitive remediation in the past 4 weeks."	Clarification that the MMSE is considered a neuropsychological assessment
Section 8.10 Visit Requirements	First paragraph describing the scheduling of the 3 visits for each testing period: change from "should be scheduled" to "must be scheduled". Correct grammar by adding "should" in this sentence: "Preferably, each cluster of 3 clinic visits should be scheduled . . ."	Revisions to emphasize the importance of scheduling the visits together in order to cluster them for each 5-consecutive days testing period and to align with the footnotes detailing this requirement in Sec 1.3 Schedule of Activities
Section 10.2 Appendix 2: Clinical Laboratory Tests	In Table 11, under "Other Screening Tests": separation of homocysteine and MMA from Vitamin B12 and folate as follows: • Vitamin B12, Folate (Homocysteine and MMA are required in case of Vitamin B12 and/or folate deficiency)	Clarification that homocysteine and methylmalonic acid tests are supplemental and only required for eligibility evaluation in case of vitamin B12 and/or folate deficiency

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Clinical Study to Evaluate a Cognitive Platform to Support Development of Symptomatic Therapies in Participants at Risk for Alzheimer's Disease

Short Title: Cognition Platform Study in Participants at Risk for Alzheimer's Disease

Acronym: N/A

Hypotheses, Objectives, and Endpoints:

The following objectives will be evaluated in participants diagnosed with mild cognitive impairment or mild Alzheimer's Disease.

Primary Objectives	Primary Endpoints
- To assess the ability of a repeated high-frequency site-based computerized cognitive assessment to evaluate the potential treatment effects of donepezil compared with placebo in participants with MCI/mild AD following a limited treatment duration (8 weeks treatment). Hypothesis: After 8 weeks of daily treatment, the change from the placebo run-in period (Week -1) in average proportion of correct responses on the One Card Learning (OCL) task (a task of visual learning) in participants receiving donepezil compared with participants receiving placebo will be ≥2 percentage points.	- Proportion of correct responses on the OCL task at Weeks -1, 2, 4, 6, and 8
Secondary Objectives	Secondary Endpoints
- To characterize the inter- and intra-subject variability associated with repeated high-frequency site-based computerized cognitive test administration in participants with MCI/mild AD. Hypothesis: The overall standard deviation associated with the change from the placebo run-in period in average OCL repeated measurements (arcsine square root transformed) after 8 weeks of donepezil treatment is ≤ 0.1.	- Proportion of correct responses on the OCL task

- To assess the ability of a repeated high-frequency site-based computerized cognitive assessment to evaluate the potential treatment effects of donepezil after 8 weeks of treatment compared to after the placebo run-in period in participants with MCI/mild AD. Hypothesis: After 8 weeks of daily treatment in participants receiving donepezil, the proportion of correct responses in the OCL task will improve relative to performance during the placebo run-in period by a clinically-meaningful (>2 percentage points) degree of change.	- Proportion of correct responses on the OCL task

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Alzheimer's Disease
Population	Participants with mild cognitive impairment or mild Alzheimer's Disease
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Placebo
Study Blinding	Single-blind (placebo run-in) followed by double-blind
Blinding Roles	Participants or Subjects, Care Provider, Investigator
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 16 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

A sufficient number of participants will be allocated/randomized such that approximately 36 evaluable participants complete the study as described in Section 9.9.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>
<table>
<tr><th>Intervention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Administra-tion</th><th>Treatment Regimen</th><th>Use</th></tr>
<tr><td rowspan="2">Active</td><td>Donepezil (Over-encapsulated)</td><td>5mg</td><td>QD</td><td>Oral</td><td>Days 1-14</td><td>Experimental</td></tr>
<tr><td>Donepezil (Over-encapsulated)</td><td>10 mg</td><td>QD</td><td>Oral</td><td>Days 15-56</td><td>Experimental</td></tr>
<tr><td>Placebo</td><td>Placebo Matching Donepezil (Over-encapsulated)</td><td>N/A</td><td>QD</td><td>Oral</td><td>Days 1-56</td><td>Experimental</td></tr>
<tr><td colspan="7">Abbreviations: QD=Once per Day; N/A=Not Applicable</td></tr>
</table>

All participants will receive placebo QD during a single-blind ~ 2-week run-in period, prior to receiving one of the 2 interventions listed in the table above during the 8-week double-blind treatment period. In the double-blind period, participants in both Intervention Groups will up-titrate following at least 14 days of dosing.
</td></tr>
<tr><td>Total Number of Intervention Groups/ Arms</td><td>2</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate for approximately 15 to 19 weeks from the time the participant provides documented informed consent through the final contact. After a screening phase ranging from approximately 3-7 weeks, each participant will be receiving assigned intervention for approximately 10 weeks: placebo run-in period of approximately 2 weeks, followed by double-blind treatment period of 8 weeks). After the end of treatment, each participant will be followed for 14 days.</td></tr>
</table>

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
There are no governance committees in this study. Regulatory, ethical, and study oversight considerations are outlined in Appendix 1.	

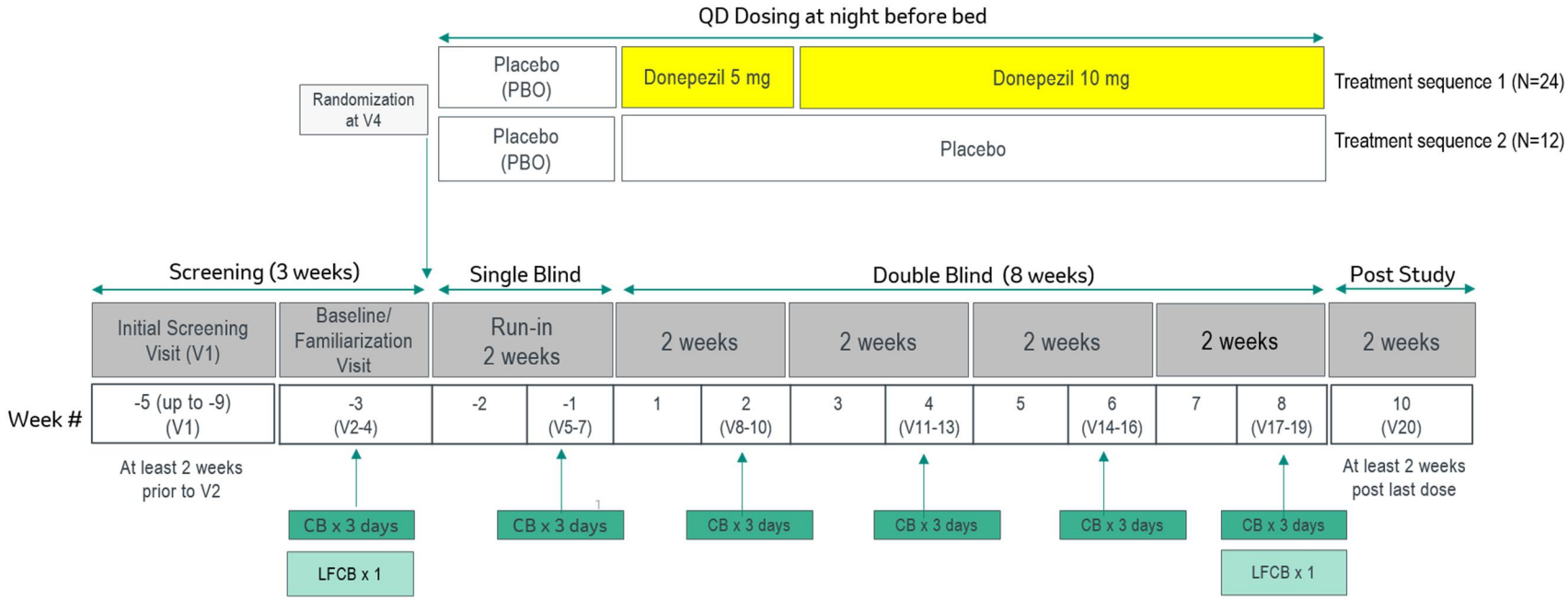
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 10.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



V=Visit
CB = Cogstate Battery Testing Period (any 3 days out of 5 consecutive days)
LFCB = Low Frequency Cognitive Battery
Randomization to occur at end of Visit 4; screening period can take up to 7 weeks to accommodate washout of prohibited medications.

1.3 Schedule of Activities

					Single-Blind			Double-Blind																	
Study Period:	Screening				Placebo Run-In			Intervention															Post-study[a]	Notes
High Frequency Testing Period[b]	**n/a**	**1**			**2**			**3**			**4**			**5**			**6**						**n/a**	Each Testing Period occurs within 5 consecutive days
Visit Number[b]/Name	**1[c]**	**2[d]** Baseline/ Familiar-ization	**3**	**4[e]** Random-ization	**5**	**6**	**7[f]**	**8**	**9**	**10[g]**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**		
Scheduled Week	-5	-3			-1			2			4			6			8			10		
Scheduled Day (d)[b]	**-32[c]**	≥14 days after V1 MMSE[d]		**-14[e]**	Within 4d prior		**1[f]**	Within 4d prior		**15[g]**	Within 4d prior		**29**	Within 4d prior		**43**	Within 4d prior		**57**	**70**	All clinic procedures are in the morning (AM). Dosing in the evening (PM).
		Within 4d prior[d]		AM PM			AM PM			AM PM												
Study Visit Window (Days)	(-30)[c]			±3[e]						+3			+3			+3			+3			
Administrative Procedures																						
Informed Consent – Study Participant	X																				Section 8.1.1.1	
Informed Consent – Study Partner/Informant	X																				Section 8.1.1.1 Study partner required for CDR assessment	
Informed Consent for FBR (Optional)	X																				Section 8.1.1.2	
Inclusion/Exclusion Criteria	X	X	X	X																	Section 8.1.2; Review against criteria in Sections 5.1, 5.2.	
Participant ID Card	X																				Section 8.1.3	
Medical History	X																				Includes substance usage: drugs, alcohol, tobacco and caffeine	
History of Neuropsychological Assessments	X																				Section 8.1.20: Any testing that may have been performed within the past 6 months	
Prior/Concomitant Medication Review	X----------X				X----------X			X---------X			X----------X										Section 5.2: Table 2	
Assignment of Screening Number	X																					

					Single-Blind				Double-Blind															
Study Period:	Screening				Placebo Run-In				Intervention														Post-study[a]	Notes
High Frequency Testing Period[b]	**n/a**	**1**				**2**				**3**				**4**			**5**			**6**			**n/a**	Each Testing Period occurs within 5 consecutive days
Visit Number[b]/Name	**1[c]**	**2[d]** Baseline/ Familiar-ization	**3**	**4[e]** Random-ization		**5**	**6**	**7[f]**		**8**	**9**	**10[g]**		**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	
Scheduled Week	-5	-3				-1				2				4			6			8			10	
Scheduled Day (d)[b]	**-32[c]**	≥14 days after V1 MMSE[d]		**-14[e]**		Within 4d prior		**1[f]**		Within 4d prior		**15[g]**		Within 4d prior		**29**	Within 4d prior		**43**	Within 4d prior		**57**	**70**	All clinic procedures are in the morning (AM). Dosing in the evening (PM).
		Within 4d prior[d]		AM	PM			AM	PM			AM	PM											
Study Visit Window (Days)	(-30)[c]			±3[e]								+3				+3			+3			+3		
Assignment of Treatment/Randomization Number				X																				Prior to dispensing first dose of study intervention (single blind placebo run-in)
Study Intervention (Placebo) Dispensing to Study Participant/Partner				X																				Instruct participant to dose with 1 capsule per night
Study Intervention (Donepezil/Placebo) Dispensing to Study Participant/Partner[h]								X				X[g]				X			X					Collect prior medication bottle before dispensing new one. Starting Visit 10, instruct participant to dose 2 capsules per night (if medication is well tolerated).
Study Intervention Dosing Diary Dispensing to Study Participant/Partner				X																				
Study Intervention (At-Home) Dose Administration/ Record in Diary[h]					X---------------X				X---------X				X--X											QD dosing, prior to retiring, at approximately same time each night. Last dose should be in the evening prior to V19.

						Single-Blind				Double-Blind															
Study Period:	Screening					Placebo Run-In				Intervention														Post-study[a]	Notes
High Frequency Testing Period[b]	**n/a**	**1**				**2**				**3**				**4**			**5**			**6**				**n/a**	Each Testing Period occurs within 5 consecutive days
Visit Number[b]/Name	**1[c]**	**2[d]** Baseline/ Familiar-ization	**3**	**4[e]** Random-ization		**5**	**6**	**7[f]**		**8**	**9**	**10[g]**		**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	
Scheduled Week	-5	-3				-1				2				4			6			8			10	
Scheduled Day (d)[b]	**-32[c]**	≥14 days after V1 MMSE[d]		**-14[e]**		Within 4d prior		**1[f]**		Within 4d prior		**15[g]**		Within 4d prior		**29**	Within 4d prior		**43**	Within 4d prior		**57**	**70**	All clinic procedures are in the morning (AM). Dosing in the evening (PM).
		Within 4d prior[d]		AM	PM			AM	PM			AM	PM											
Study Visit Window (Days)	(-30)[c]			±3[e]								+3				+3			+3			+3		
Study Intervention Compliance/Diary Review						X	X	X		X	X	X[g]		X	X	X	X	X	X	X	X	X		
MHIS	X																							Section 8.1.13
MMSE[i]	X	X[d]																						Section 8.1.14; the 2 assessments should be performed by the same rater and administered at least 2 weeks apart.
CDR Scale [i,j]	X																							Section 8.1.15
GDS – 15 Item	X																							Section 8.1.16
MRI[k]	X																							Section 8.1.17
Domiciling (Optional)[h,l]		X	X	X		X	X	X		X	X	X		X	X	X	X	X	X	X	X	X		Cognitive Testing to be done for 3 consecutive days if kept domiciled
Participant/Study Partner Questionnaire (Optional)[m]																X					X[m]			Section 8.1.19; Survey regarding Remote Cognitive Testing
Safety Procedures																								
Full Physical Examination	X																						X	Section 8.3.1
Height	X																							
Weight	X																							BMI to be taken at screening

						Single-Blind				Double-Blind																
Study Period:	Screening					Placebo Run-In				Intervention															Post-study[a]	Notes
High Frequency Testing Period[b]	**n/a**	**1**				**2**				**3**				**4**			**5**			**6**				**n/a**	Each Testing Period occurs within 5 consecutive days
Visit Number[b]/Name	**1[c]**	**2[d]** Baseline/ Familiar-ization	**3**	**4[e]** Random-ization		**5**	**6**	**7[f]**		**8**	**9**	**10[g]**		**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	
Scheduled Week	-5	-3				-1				2				4			6			8			10	
Scheduled Day (d)[b]	**-32[c]**	≥14 days after V1 MMSE[d]		**-14[e]**		Within 4d prior		**1[f]**		Within 4d prior		**15[g]**		Within 4d prior		**29**	Within 4d prior		**43**	Within 4d prior		**57**	**70**	All clinic procedures are in the morning (AM). Dosing in the evening (PM).
		Within 4d prior[d]		AM	PM			AM	PM			AM	PM											
Study Visit Window (Days)	(-30)[c]			±3[e]								+3				+3			+3			+3		
Targeted Neurological Examination	X																							Section 8.3.2 and Appendix 9. Mental status module is covered by MMSE.
Vital Signs (Heart Rate, Blood Pressure)	X																						X	Section 8.3.3
Respiratory Rate	X																						X	
Body Temperature	X																						X	
12-lead ECG[n]	X																							Section 8.3.4
Serum FSH - (as needed in postmenopausal females only)	X	X[o]																						Appendix 5
RPR	X																							Appendix 2
HIV, hepatitis B and C screen	X																							Appendix 2
UDS	X																							Appendix 2
Hematology	X																						X	Appendix 2
Urinalysis	X																						X	Appendix 2
Chemistry	X																						X	Appendix 2; Includes at screening: TSH, Vitamin B12, Folate, Homocysteine, and MMA
AE/SAE review	X----------X					X----------X				X--------X				X----------X										
C-SSRS Screening	X																							Section 8.3.6
C-SSRS Since Last Visit				X				X				X				X			X			X	X	Section 8.3.6

					Single-Blind			Double-Blind																	
Study Period:	Screening				Placebo Run-In			Intervention															Post-study[a]	Notes
High Frequency Testing Period[b]	**n/a**	**1**			**2**			**3**			**4**			**5**			**6**			**n/a**	Each Testing Period occurs within 5 consecutive days				
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Scheduled Week	-5	-3			-1			2			4			6			8			10					
Scheduled Day (d)[b]	**-32[c]**	≥14 days after V1 MMSE[d]		**-14[e]**	Within 4d prior		**1[f]**	Within 4d prior		**15[g]**	Within 4d prior		**29**	Within 4d prior		**43**	Within 4d prior		**57**	**70**	All clinic procedures are in the morning (AM). Dosing in the evening (PM).				
		Within 4d prior[d]		AM	PM		AM	PM		AM	PM														
Study Visit Window (Days)	(-30)[c]			±3[e]						+3			+3			+3			+3					
Pharmacokinetics																									
Blood for Plasma Donepezil Assay										X			X						X		Sections 8.6, 8.9			
Pharmacodynamics																									
Computerized Cognitive Assessment with Cogstate Brief Battery[p,q]		X[p]	X	X		X	X	X		X	X	X		X	X	X	X	X	X	X	X	X	X		Section 8.7.1: Detection (DET), Identification (IDN), One-Card Learning (OCL), One Back (ONB)
Computerized Cognitive Assessment with additional Tests from Cogstate Battery:																									Section 8.7.1
International Shopping List Test-Learning Trials		X	X	X		X	X	X		X	X	X					X	X	X	X	X	X			ISLT – 12 words
Modified Groton Maze Learning Test		X	X	X		X	X	X		X	X	X					X	X	X	X	X	X			GMLTM
Continuous Paired Associate Learning		X	X	X		X	X	X		X	X	X					X	X	X	X	X	X			CPAL
International Daily Symbol Substitution Test -Medicines		X	X	X		X	X	X		X	X	X					X	X	X	X	X	X			IDSSTM
International Shopping List Test -Delayed Recall		X	X	X		X	X	X		X	X	X					X	X	X	X	X	X			ISRL- 12 words
Face Name Associative Memory Exam		X	X			X	X			X	X			X	X		X	X		X	X				FNAME

					Single-Blind			Double-Blind															
Study Period:	Screening				Placebo Run-In			Intervention														Post-study[a]	Notes
High Frequency Testing Period[b]	**n/a**	**1**			**2**			**3**			**4**			**5**			**6**				**n/a**	Each Testing Period occurs within 5 consecutive days
Visit Number[b]/Name	**1[c]**	**2[d]** Baseline/ Familiar-ization	**3**	**4[e]** Random-ization	**5**	**6**	**7[f]**	**8**	**9**	**10[g]**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**		**20**	
Scheduled Week	-5	-3			-1			2			4			6			8				10	
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		Within 4d prior[d]		AM PM			AM PM			AM PM												
Study Visit Window (Days)	(-30)[c]			±3[e]						+3			+3			+3			+3			
Low Frequency Cognitive Battery[r]:																						Sections 8.7.2, 8.7.3, 8.7.4
FCSRT[s]			X															X				Picture version with Immediate and Delayed Recall
WAIS-IV-Coding			X															X				
Verbal Fluency Test[t]			X															X				D-KEFS subscale
Sorting			X															X				D-KEFS subscale
Twenty Questions			X															X				D-KEFS subscale
Biomarkers																						
Blood for Genetic Analysis				X																		Sections 8.8, 8.9. Collect predose from enrolled participants only.
Blood for APOE genotyping				X																		Sections 8.8, 8.9. Collect predose from enrolled participants only and in a separate tube from the sample taken for Genetic Analysis.
Blood for Exploratory Plasma Biomarkers for AD Diagnosis				X[u]															X			Sections 8.8, 8.9.

					Single-Blind			Double-Blind															
Study Period:	Screening				Placebo Run-In			Intervention													Post-study[a]	Notes
High Frequency Testing Period[b]	**n/a**	**1**			**2**			**3**			**4**			**5**			**6**			**n/a**	Each Testing Period occurs within 5 consecutive days	
Visit Number[b]/Name	**1[c]**	**2[d]** Baseline/ Familiar-ization	**3**	**4[e]** Random-ization	**5**	**6**	**7[f]**	**8**	**9**	**10[g]**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**		
Scheduled Week	-5	-3			-1			2			4			6			8			10		
Scheduled Day (d)[b]	**-32[c]**	≥14 days after V1 MMSE[d]		**-14[e]**	Within 4d prior		**1[f]**	Within 4d prior		**15[g]**	Within 4d prior		**29**	Within 4d prior		**43**	Within 4d prior		**57**	**70**	All clinic procedures are in the morning (AM). Dosing in the evening (PM).	
		Within 4d prior[d]		AM PM			AM PM			AM PM												
Study Visit Window (Days)	(-30)[c]			±3[e]						+3			+3			+3			+3			

AD=Alzheimer's Disease; AE=adverse event; APOE=Apolipoprotein E; CDR=Clinical Dementia Rating; C-SSRS=Columbia-Suicide Severity Rating Scale; D-KEFS= Delis-Kaplan Executive Function System; ECG=electrocardiogram; FBR=future biomedical research; FSH=follicle stimulating hormone; FCSRT=Free and Cued Selective Reminding Test; GDS=Geriatric Depression Scale; HIV=human immunodeficiency virus; ID=identification; MHIS=Modified Hachinski Ischemia Scale; MMA=methylmalonic acid; MMSE=Mini Mental State Examination; MRI=Magnetic Resonance Imaging; RPR=Rapid Plasma Reagin; SAE=serious adverse event; UDS=Urine Drug Screen; WAIS=Wechsler Adult Intelligence Scale

a. Poststudy visit procedures should also be performed for participants who discontinued early from study intervention.

b. The 3 visits for each weekly testing period will be scheduled together, with the first 2 visits scheduled within 5 days of the last testing visit in that week. For example, Visits 2 and 3 are anchored by the date when Visit 4 is scheduled; they will be scheduled on any one of the 4 days prior to Visit 4 Randomization. Similarly, Visits 5 and 6 are anchored by the date when Visit 7 is scheduled; they will be scheduled on any one of the 4 days prior to Visit 7. Preferably, each cluster of 3 clinic visits will be scheduled within a single working week (which could include the following [not preceding] Saturday if the clinic is open and staffed appropriately). It is recommended that the site schedule all study visits in advance when a participant is deemed eligible based on Visit 1 results. If the +3 days permissible study visit window is used for the anchor visit (i.e. third visit of each testing period), the first 2 visits of that testing period will still need to occur within 4 days prior to the anchor visit.

c. Screening Visit 1 assessments may be conducted over the course of more than 1 day to decrease participant/study partner burden (See Section 8.10.1 for details). The visit window for Screening Visit 1 is provided to accommodate up to a 30-day washout period for prohibited medications, resolve/stabilize any conditions or treatments, provide flexible scheduling, and repeat of study procedures, if needed. If Visit 1 is split for washing out prohibited medications, then the initial portion of Visit 1 would occur on Day -62 and the final portion of Visit 1 will occur on Day -32, which is when the clinical and cognitive assessments (MMSE, CDR, MHIS, GDS, and C-SSRS) should be performed.

d. Visit 2 Baseline/Familiarization is the first clinic visit for the first testing cluster and is anchored by the date when Visit 4 (Randomization) is scheduled; Visits 2 and 3 should be scheduled within the 4 days prior to Visit 4. In addition, since MMSE is repeated at Visit 2 following the first screening MMSE, Visit 2 should be scheduled at least 2 weeks from the first Screening visit when the first MMSE is performed (see Manual of Assessments [MOA] for details related to alternate words which should be used at Visit 2 to minimize practice effects).

e. Visit 4 will be scheduled at approximately 2 weeks prior to Study Day 1 (Visit 7), within the permissible window of ±3 days for Visit 4 to occur between Study Day -11 to -17. If the ±3 day permissible window is used for Visit 4, then Visits 2 and 3 must still be scheduled within 4 days prior to Visit 4.

f. Study Day 1 is anchored by the date of the first dose of the double-blind period (in the evening of Visit 7). The Scheduled Week and Study Day in this SoA are to be used as internal reference by the sponsor and study site staff when scheduling participant visits. From the participant and study partner's perspective, they are participating in a single intervention period. Study participants should only be aware of the High Frequency Cognitive Testing Period number, Visit number, and the corresponding calendar date the visit falls on.

g. If Visit 10 is scheduled on Study Day 15, the site should call the day before and ensure patient compliance with QD dosing prior to this visit. If patient has skipped a dose during this 2-week period, Visit 10 should be rescheduled within permissible window +3, to ensure participants have demonstrated tolerability prior to instructing participants to up-titrate study medications following this visit.

					Single-Blind			Double-Blind															
Study Period:	Screening				Placebo Run-In			Intervention													Post-study[a]	Notes	
High Frequency Testing Period[b]	**n/a**	**1**			**2**			**3**			**4**			**5**			**6**			**n/a**	Each Testing Period occurs within 5 consecutive days	
Visit Number[b]/Name	**1[c]**	**2[d]** Baseline/ Familiar-ization	**3**	**4[e]** Random-ization	**5**	**6**	**7[f]**	**8**	**9**	**10[g]**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**		
Scheduled Week	-5	-3			-1			2			4			6			8			10		
Scheduled Day (d)[b]	**-32[c]**	≥14 days after V1 MMSE[d]		**-14[e]**	Within 4d prior		**1[f]**	Within 4d prior		**15[g]**	Within 4d prior		**29**	Within 4d prior		**43**	Within 4d prior		**57**	**70**	All clinic procedures are in the morning (AM). Dosing in the evening (PM).	
		Within 4d prior[d]		AM PM			AM PM			AM PM												
Study Visit Window (Days)	(-30)[c]			±3[e]						+3			+3			+3			+3			

h. For participants who are kept domiciled for the duration of the 3-day testing period, the study staff will witness the dose administration when participants are in the CRU and work with the participants on the completion of the study intervention dosing diary.

i. The MMSE and CDR should be submitted to the rater training vendor the same day they are administered.

j. The CDR must be administered by a qualified rater who is not involved with other assessments at Screening Visit 1. The study partner should be interviewed first, followed by the participant (see MOA).

k. Previous scans performed within 1 year of signing ICF may be used in lieu of a screening scan, provided the scans themselves or the report of the scan are made available to the investigator for assessment of study eligibility. If a new MRI needs to be performed, it should be scheduled to occur after participant has met all other study eligibility criteria at Visit 1

l. Only for sites with capability to keep participants overnight and if in the opinion of the investigator and study participant, domiciling is preferable to daily visits to the clinic- in which case the 3 days of cognitive testing should be on consecutive days. Participants would be discharged after completion of study procedures on the 3rd day of each testing period. The study partner is not required to spend the night but may do so depending on the participant.

m. Participant only completes questionnaire at Visit 13. Both participant and study partner are to complete at Visit 18. If the Low Frequency Cognitive Battery (LFCB) was administered across 2 days (e.g. Visits 18 & 19), then questionnaire should be administered at Visit 19. The study partner completing the questionnaire should be the same individual that completed the CDR assessment at the Screening visit. The study partner portion of the questionnaire maybe completed by phone if he/she did not accompany the study participant to the visit.

n. Previous ECG performed within 3 months of signing ICF may be used in lieu of a screening ECG, provided the ECG report is made available to the investigator for assessment of study eligibility.

o. A repeat FSH measurement is required at Visit 2 to confirm postmenopausal status if duration of amenorrhea is less than 12 months. Refer to Appendix 5.

p. At each visit during each weekly testing period, the computerized cognitive assessments with the Cogstate Brief Battery (CBB) should be administered first followed by the additional tests in the Cogstate Battery) before performing any other clinic procedures.

q. At Visit 2, participants will perform the CBB: (DET, IDN, OCL, ONB) 2 times. Each set of CBB assessments should be separated by a rest period of approximately 15 minutes. Participants will continue with the rest of the computerized cognitive assessments on the Cogstate Battery after completing the second set of the CBB and after they are determined to be eligible based on the results as reported by Cogstate (see Inclusion Criterion #16).

					Single-Blind			Double-Blind														
Study Period:	Screening				Placebo Run-In			Intervention													Post-study[a]	Notes
High Frequency Testing Period[b]	**n/a**	**1**			**2**			**3**			**4**			**5**			**6**			**n/a**	Each Testing Period occurs within 5 consecutive days
Visit Number[b]/Name	**1[c]**	**2[d]** Baseline/ Familiar-ization	**3**	**4[e]** Random-ization	**5**	**6**	**7[f]**	**8**	**9**	**10[g]**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	
Scheduled Week	-5	-3			-1			2			4			6			8			10	
Scheduled Day (d)[b]	**-32[c]**	≥14 days after V1 MMSE[d]		**-14[e]**	Within 4d prior		**1[f]**	Within 4d prior		**15[g]**	Within 4d prior		**29**	Within 4d prior		**43**	Within 4d prior		**57**	**70**	All clinic procedures are in the morning (AM). Dosing in the evening (PM).
		Within 4d prior[d]		AM PM			AM PM			AM PM											
Study Visit Window (Days)	(-30)[c]			±3[e]						+3			+3			+3			+3		

r. The LFCB assessments may be conducted over the course of more than 1 day (i.e. Visits 3-4; and Visits 18-19) to decrease participant burden (See Section 8.10.2 for details on recommendation for splitting the visit). The rater should ensure consistency in the administration of the LFCB during the course of the study. If the screening/pre-treatment LFCB was performed over 2 days for an individual participant at Visits 3-4, then the LFCB scheduled for the later timepoint (i.e.Visit 18) should also be consistently split across 2 days (i.e. Visits 18-19).

s. For FCSRT, no other cognitive assessments can be performed during the 20-30 min interval between Trial 3 of Free and Cued Recall and the start of Delayed Recalled portion of the FCSRT. The participant will be given another short break during this time.

t. For the Verbal Fluency Test, only the letter fluency and category fluency tasks will be administered.

u. Alternately, blood for biomarkers for AD diagnosis may be collected at the next scheduled blood draw at either Visit 10 or Visit 13 (to coincide with the blood collection for the donepezil assay).

2 INTRODUCTION

2.1 Study Rationale

Drug development for symptomatic therapies in AD is burdened by significant time and cost to assess the potential efficacy of new drugs. Proof-of-concept studies for new drugs rely on demonstrating improvement on clinical cognition measures such as the ADAS-Cog. However, many of these clinical endpoints are bound by limited sensitivity to disease progression and/or drug response. As a result, large sample sizes and long treatment duration (typically ≥ 3-6 months) are required to provide sufficient statistical power to begin to establish efficacy. Moreover, pathophysiological changes secondary to AD lead to cognitive fluctuations that create variability in patient cognitive performance and thus in assessment of cognition endpoints. Thus, assessment of cognitive pharmacodynamic effects using these standard measurements in small patient populations is not feasible.

Consequently, there is an urgent need for novel clinical trial methodology that will support high-predictive value decision-making in the early clinical development environment to trigger investment in fully-powered symptomatic trials. The rationale for this study is to assess whether one candidate methodology is viable. This methodology would have the ability to interrogate and assess probability of benefit of pro-cognitive effects of investigational compounds in a relatively low number of patients affected by AD pathology, in a relative rapid manner to improve clinical throughput, make better Phase 1 triaging decisions across different mechanisms, and reduce the number of low-probability of success compounds advanced for testing in Phase 2.

2.2 Background

The overall objective of this study is to rigorously test a novel high-frequency “burst” testing paradigm designed to leverage the repeatability of computerized batteries for a precise assessment of cognitive capability, as a means to assess pro-cognitive pharmacodynamic potential in one or two key sentinel cognitive domains with strong face validity for predicting efficacy in more standard assessment tools. Donepezil will be used as the investigational agent in this study as it is the most commonly prescribed cholinesterase inhibitor prescribed for symptomatic treatment of AD. As such, it is anticipated that treatment effect data on donepezil obtained through this study can be used as benchmarking data for evaluation of performance of future pro-cognitive compounds being assessed using this high-frequency testing paradigm.

2.2.1 Information on Study-Related Therapy

The most common AEs of donepezil, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day and occurring at twice the rate observed in placebo treated participants, are largely predicted by the cholinomimetic effects of donepezil HCl. These include nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue and anorexia. These AEs are typically of mild intensity and transient, resolving during continued donepezil HCl treatment without the need for dose modification [Jackson, S., et al 2004]. Less-commonly

observed AEs include depression and sleep disturbances (e.g., abnormal dreams and somnolence).

Donepezil is ~ 96% bound to human plasma proteins, mainly to albumins (~ 75%) and alpha-1 acid glycoprotein (about 21%) over the concentration range of 2 to 1000 ng/mL. Donepezil is both excreted in the urine intact and extensively metabolized to four major metabolites, two of which are known to be active, and a number of minor metabolites, not all of which have been identified. Donepezil is metabolized by CYP 450 isoenzymes 2D6 and 3A4 and undergoes glucuronidation. Donepezil has a Tmax of ~3 to 4 hours and half-life ~ 70 hours.

Refer to the approved labeling for additional detailed background information on donepezil [U.S. Prescribing Information 2018].

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in experimental medicine will directly benefit from participation, as these studies are designed to provide information about the safety and effectiveness of an investigational procedure.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

The following objectives will be evaluated in participants diagnosed with mild cognitive impairment or mild Alzheimer's Disease.

Objectives	Endpoints
Primary	
• To assess the ability of a repeated high-frequency site-based computerized cognitive assessment to evaluate the potential treatment effects of donepezil compared with placebo in participants with MCI/mild AD following a limited treatment duration (8 weeks treatment). **Hypothesis:** After 8 weeks of daily treatment, the change from the placebo run-in period (Week -1) in average proportion of correct responses on the One Card Learning (OCL) task (a task of visual learning) in participants receiving donepezil compared with participants receiving placebo will be ≥2 percentage points.	• Proportion of correct responses on the OCL task at Weeks -1, 2, 4, 6, and 8

Objectives	Endpoints
Secondary	
• To characterize the inter- and intra-subject variability associated with repeated high-frequency site-based computerized cognitive test administration in participants with MCI/mild AD. **Hypothesis:** The overall standard deviation associated with the change from the placebo run-in period in average OCL repeated measurements (arcsine square root transformed) after 8 weeks of donepezil treatment is ≤ 0.1.	• Proportion of correct responses on the OCL task
• To assess the ability of a repeated high-frequency site-based computerized cognitive assessment to evaluate the potential treatment effects of donepezil after 8 weeks of treatment compared to after the placebo run-in period in participants with MCI/mild AD. **Hypothesis:** After 8 weeks of daily treatment in participants receiving donepezil, the proportion of correct responses in the OCL task will improve relative to performance during the placebo run-in period by a clinically-meaningful (>2 percentage points) degree of change.	• Proportion of correct responses on the OCL task

Objectives	Endpoints
Tertiary/Exploratory	
• To characterize the inter- and intra-subject variability associated with repeated high-frequency site-based computerized cognitive test administration in participants with MCI/mild AD.	• Detection (DET), Identification (IDN), One Back (ONB), International Shopping List Test (ISLT), Modified Groton Maze Learning Test (GMLTM), Continuous Paired Associate Learning (CPAL), International Daily Symbol Substitution Test - Medicines (IDSSTM), International Shopping List Test - Delayed Recall (ISRL) at Weeks -1, 2, 4, 6, and 8
• To assess the ability of a repeated high-frequency site-based computerized cognitive assessment to evaluate the potential treatment effects of donepezil after 8 weeks of treatment compared to after the placebo run-in period in participants with MCI/mild AD.	• DET, IDN, ONB, ISLT, GMLTM, CPAL, IDSSTM, ISRL at Weeks -1, 2, 4, 6, and 8
• To assess the ability of a repeated high-frequency site-based computerized cognitive assessment to evaluate the potential treatment effects of donepezil compared with placebo on tests associated with cognitive domains of attention, executive function and verbal/ visual memory in participants with MCI/ mild AD following 8 weeks of treatment.	• DET, IDN, ONB, ISLT, GMLTM, CPAL, IDSSTM, ISRL at Weeks -1, 2, 4, 6, and 8
• To evaluate the psychometric properties of the Face-Name Associative Memory Exam (FNAME) as a measure of learning.	• FNAME
• To establish the operational feasibility of frequent site-based administration of cognitive function testing in participants with MCI/mild AD.	• Study Execution

Objectives	Endpoints
• To assess participants' and study partner/informants' perception and comfort with the use of at-home device (e.g. tablet/computer) in future studies.	• Questionnaires
• To evaluate the differences in baseline cognitive performance and response to donepezil treatment (comparison to placebo and to pre-treatment baseline) between different participant subgroups defined by positive and negative results for various exploratory plasma biomarkers for AD diagnosis.	• Plasma levels of beta-amyloid and phospho-tau isoforms
• To assess within-subject test-retest reliability of various exploratory plasma biomarkers for AD diagnosis in replicate samples taken during the study.	• Plasma levels of beta-amyloid and phospho-tau isoforms
• To explore the relationship between genetic variation and 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.	• Apolipoprotein E (APOE) genotyping • Germline genetic variation and association to clinical data collected in this study.

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, placebo-controlled, parallel-group, multi-site study to evaluate the effects of donepezil 10 mg PO daily on cognitive function using a high-frequency site-based computerized cognitive assessment, the Cogstate Computerized Battery, in participants with MCI or mild AD.

The study will enroll approximately 36 participants randomized to receive over-encapsulated donepezil or placebo in a 2:1 ratio following a single blinded run-in period with placebo. No formal stratification is planned per site; however, an allocation schedule with separate panels for disease status (ie, Panel A for MCI and Panel B for mild AD) will be used with each panel incorporating randomization in a 2:1 ratio. Efforts will be made to enroll a minimum of 12 participants meeting AD diagnostic criteria (Panel B) in this study. The number of participants per panel (ie, disease status) may be adjusted by the Sponsor based on

enrollment metrics to ensure timely study completion, but the total sample size of the study will remain at approximately 36. The rationale for ensuring this minimum number of participants meeting AD criteria is that prior data suggest a more robust treatment signal for OCL testing in this population, and ensuring adequate representation of mild AD in the overall study sample will increase probability of study success.

Potential participants will have a Screening Visit (V1) to determine if they meet inclusion and exclusion criteria. Following the Screening Visit, participants will have a Baseline/Familiarization Visit (V2), during which the Cogstate battery will be administered for familiarization purposes as described in Section 1.3 (SoA). Participants who met the selection criteria at that point will return for 2 additional visits (V3 and V4) during that week, when a Cogstate battery as described in Section 1.3 (SoA) will be administered to further acclimate them to the high-frequency testing paradigm, and to provide a standard replicate testing period consistent with a mock baseline assessment initiating the placebo run-in period. As part of the testing during this week, participants will also undergo additional paper/pencil cognitive baseline (pre-treatment) assessment for the purposes of characterization of baseline cognitive status across several different performance domains before randomization into one of two treatment sequences.

After the Randomization Visit (V4), participants will enter a single-blind placebo run-in period of approximately 2 weeks. During the second week of the placebo run-in period, participants will undergo a high-frequency testing period with a Cogstate battery as described in Section 1.3 (SoA). This testing period will cover 3 clinic visits (V5-7) over the span of 5 consecutive days. Testing will be administered on-site.

After completing the placebo run-in period, participants will enter a double-blind intervention period of approximately 8 weeks and initiate treatment with either over-encapsulated donepezil or placebo. Participants allocated to donepezil will be given donepezil 5 mg PO daily for approximately 2 weeks (at least 14 days), followed by titration to donepezil 10 mg PO daily depending on tolerability. Once titrated to donepezil 10 mg PO daily, participants will remain on this daily dose for 6 weeks. To maintain the study blind, participants allocated to placebo will follow the same dose titration regimen. Participants will return to the clinic at two-week intervals during the treatment period, to undergo computerized Cogstate testing following the high-frequency schedule as described in Section 1.3 (SoA) (at V8-10, V11-13, V14-16, and V17-19). The paper/pencil based cognitive battery (which was administered at baseline prior to randomization) will be administered a second time at the End of Treatment Visit (V19). A Post-Study Visit (V20) will be conducted at least 14 days after the last dose of study drug.

This protocol is written with flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Refer to Section 8.10.5 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

Rationale for High-Frequency Computerized Test Administration

Over the past decade, successive external and internal studies have progressively evaluated the ability of repeated, high-frequency computerized cognitive testing to identify potential treatment effects of pro-cognitive compounds in small study populations over a limited treatment duration. Based on these studies, the high-frequency testing methodology is believed to improve measurement precision with enhanced sensitivity to detect cognitive change. Overall, the idea of high frequency testing is based on the premise that patients with AD pathology typically have significant fluctuations in cognitive performance over time, and even on a daily basis. As a result, solitary assessments of cognition conducted several months apart (as typically done with the ADAS-Cog, for example) may not accurately assess a patient's true mean cognitive baseline or their true mean cognitive performance after several months of treatment with a symptomatic pro-cognitive compound. However, if cognitive testing could be conducted more frequently, individual test variability could have less impact on overall performance, supporting more accurate determination of true baseline cognition and providing more reliable results of potential treatment effect.

Previously, AstraZeneca conducted a study (CogMemo) in collaboration with Cogstate Ltd. in patients with mild to moderate AD, in which a standardized computerized test battery (Cogstate) as well as a standardized paper/pencil battery (ADAS-Cog and the NTB) were administered to participants multiple times on a monthly basis to obtain an assessment of baseline cognition, followed by repeated testing around the time of efficacy at 4, 8 and 12 weeks of treatment with donepezil. Group differences were detected after 8 and 12 weeks of treatment when applying individual Cogstate tests, but not using more conventional cognitive assessments, such as ADAS-Cog and the NTB. These results seemed to support the idea that providing a standard, computerized battery with multiple forms (to minimize practice and learning effects after repeated administration) with the potential for reduced examiner-induced variability, could improve the ability to detect a treatment signal in a smaller population over a short duration of treatment. In particular, the OCL, a measure of visual learning in the Cogstate Battery was able to demonstrate a statistically-significant treatment effect following monthly administration.

A follow-up Merck experimental medicine study (MK-0000-318) conducted in conjunction with Cogstate Ltd. included repeated testing of increased frequency (~ 5 in-home test administrations over a 7-day test period, conducted at baseline and repeated monthly after 1, 2 and 3 months of treatment) in participants with MCI and participants with mild AD treated with donepezil versus placebo. Cogstate tests were conducted in the presence of a trained testing supervisor in the participants' homes in order to ensure a consistent test environment, support participant motivation, and assist with technical challenges. The primary objective of the study was to evaluate inter- and intra-subject variability following repeated administration of the Cogstate battery, particularly the OCL test. The secondary objective of the study was to evaluate a potential treatment effect among donepezil-treated participants, comparing change in performance on the OCL test after 12 weeks of treatment with OCL performance at baseline. The study achieved both objectives, demonstrating low inter- and

intra-subject variability and a relative improvement in OCL performance within donepezil-treated participants following 12 weeks of treatment. These results further supported the idea that high-frequency computerized test administration improves the potential to detect a symptomatic pro-cognitive effect in smaller participant populations over a limited duration of treatment. However, there were some limitations with the study. First, while 36 total participants were included in the study, only a limited number of participants (N=6) were allocated to treatment with placebo, precluding extensive analysis of treatment effects between donepezil- and placebo-treated participants. Second, operational challenges of locating treatment-naïve participants with MCI and AD combined with difficulties with locating site staff willing to travel to participants' homes and subsequent coordination of home supervisor/participant scheduling led to extended recruitment timelines and required 26 months to complete the study.

The current study will build on these prior evaluations and respond to previously- identified challenges. Like the CogMemo study and MK-0000-318, it will include a limited number of study participants in an affected patient population of participants with MCI and mild AD. Like the CogMemo and MK-0000-318 studies, this study will include high-frequency repeated administration of a computerized test battery (Cogstate). However, in contrast to MK-0000-318, in which supervised testing was conducted in participants' homes, this study will conduct cognitive testing in the clinic. This shift is hypothesized to help standardize the test environment and mitigate sources of variability in at-home testing scenarios that may impede determination of a potential treatment effect signal. The recruitment and retention benefit of ensuring trained test administrators could engage participants directly in their homes was also not deemed sufficient rationale for continuing to pursue this approach due to its overall operational complexity.

The overall study duration for an individual participant will be approximately 15-19 weeks from Screening to Post-Study Visit, compared with 24 weeks for MK-0000-318.

Rationale for Study Treatment Duration

While the MK-0000-318 study evaluated the Cogstate effects of 12 weeks of treatment with donepezil (including 2 weeks of treatment with 5 mg PO daily, followed by 10 weeks of treatment with donepezil 10 mg PO daily), post-hoc analyses of donepezil treatment effect in the study data indicate that the earliest potential treatment effect may be seen following a minimum of 6 total weeks of treatment with donepezil, including 2 weeks treatment with donepezil 5 mg PO daily followed by titration up to 10 mg PO daily for 4 weeks. Additional positive treatment efficacy was observed following longer durations of donepezil treatment (10- and 14- weeks).This study will include an 8-week donepezil treatment duration, including an initial 2 weeks treatment with donepezil 5 mg PO daily followed by titration up to 10 mg PO daily for 6 weeks. The rationale for this treatment duration is to minimize the overall exposure for participants in the study, but also to ensure sufficient treatment duration (i.e. > 6 weeks, based on MK-0000-318 findings) to maximize probability of observing efficacy.

Rationale for Test Frequency

Subjects will participate in repeated test assessment periods approximately every two weeks after initiating treatment. The two-week interval was selected based on the t1/2 of donepezil, which is approximately 70 hours and as a result is expected to reach steady-state concentrations after approximately two weeks of daily dosing. Assessments conducted after Week 2 in the Treatment Period are expected to assess potential treatment effect once steady-state PK is reached for donepezil 5 mg PO daily; assessments at Week 4 in the Treatment Period will assess potential treatment effects once steady-state PK is reached for donepezil 10 mg PO daily; and assessments at Week 8 will assess treatment effects at a timepoint following the minimal treatment duration following which a treatment effect signal was observed in MK-0000-318.

As in MK-0000-318, participants in this study will complete multiple test administrations for each test period (Weeks 2, 4, 6, 8, 10). The number of repeated assessments is based on the minimum number of daily assessments required to ensure adequate test reliability and treatment effect response as estimated from the MK-0000-318 data.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

There are no direct efficacy assessments in this study.

4.2.1.2 Safety Endpoints

Safety for all participants will be assessed throughout the study by monitoring for clinical AEs, including physical/neurological examinations, C-SSRS, VS, and laboratory safety tests (serum chemistry, hematology, and urinalysis).

4.2.1.3 Pharmacokinetic Endpoints

To enable the use of plasma concentrations to explain effects on safety and pharmacodynamic endpoints observed, plasma samples will be collected during the study for measuring donepezil concentrations as needed.

4.2.1.4 Pharmacodynamic Endpoints

Computerized Cognitive Assessment with the Cogstate Battery

Cogstate computerized cognition testing has been developed and tested over the years as a standardized, easy-to-deploy solution to assess human cognitive function across various domains, with minimal reliance on rater training for test administration. Although computerized cognition testing batteries were developed for periodic usage, their high number of testing versions and lack of learning effects makes them ideal candidate for evaluation in high-frequency, repetitive testing paradigms as well. This study will utilize the Cogstate Brief Battery (CBB), which includes the primary endpoint OCL testing, as the core

testing battery; this study will also evaluate other Cogstate tests in a similar high-frequency paradigm.

The CBB is designed to be sensitive to the various domains of cognitive impairments that characterize AD patients yet simple enough for individuals with cognitive impairment to complete without requiring great support or assistance. The specific modules for this Battery (DET, IDN, OCL, ONB) emphasize the assessment of attention, processing speed, episodic memory, and working memory, all of which are typically impaired in amnestic MCI and early AD.

The OCL task has been selected as the primary endpoint for the primary and secondary objectives because: (1) OCL is a test of episodic memory, the primary deficit in mild AD; (2) OCL was the most sensitive measure to detect a treatment effect in the CogMemo and MK-0000-318 studies; and (3) OCL was the most sensitive measure to detect cognitive decline in an observation study in participants with very early AD. As such, it is an ideal sentinel cognitive domain to interrogate for signs of relevant pharmacodynamic activity in AD patients.

The potential treatment effects generated on other cognitive endpoints evaluating domains of attention, executive function and visual/ verbal memory will be evaluated as exploratory endpoints in order to support future use of this platform for compounds that may have a different mechanism of action from donepezil.

The additional modules aside from those included in the CBB selected for this study were identified in conjunction with Cogstate, to appropriately measure the cognitive domains of attention, executive function and verbal/ visual memory while preserving test efficiency and reducing test length. The combined modules (CBB + additional modules) take approximately 30-45 minutes to complete. The selected tasks for this study are outlined in Table 1.

Table 1 Description of Outcome Measures for the Cogstate Battery

Test Name	Main Cognitive Domain	Unit of Measurement	Description of Outcome
Cogstate Brief Battery			
Detection Task	Psychomotor function	Speed (msecs)	Speed of performance; mean of the log_{10} transformed reaction times for correct responses Lower score = better performance
Identification Task	Attention	Speed (msecs)	Speed of performance; mean of the log_{10} transformed reaction times for correct responses Lower score = better performance
One Card Learning Test	Visual Learning	Accuracy (arcsin proportion correct)	Number of correct recognitions of previously seen stimuli
One Back Test	Working memory	Accuracy (arcsin proportion correct)	Number of correct recognitions of previously seen stimuli
Additional Testing Modules			
International Shopping List Test – Learning Trials	Verbal learning	Accuracy (n words)	Number of words recalled successfully across the three learning trials
International Shopping List Test – Delayed Recall	Verbal memory	Accuracy (n words)	Number of words recalled successfully after the delay
Modified Groton Maze Learning Test	Executive function	Number of errors	Number of errors made while learning the location of a hidden pathway over 5 consecutive trials
Continuous Paired Associate Learning	Visual Learning	Accuracy (n errors)	Number of errors made in learning associations between six patterns and six locations
International Daily Symbol Substitution Test	Complex Attention	Accuracy (n correct)	N correct symbols placed under their numbers in accord with the key
Face Name Associative Memory Exam	Learning	Accuracy (number correct)	Number of correct pairings over 12 trials

Low Frequency Cognitive Battery

Additional paper/pencil cognitive assessments will be administered at a low frequency at baseline (pre-treatment) and at the end of treatment; these measures are referred to as the Low Frequency Cognitive Battery (LFCB) in this study. Broadly, the LFCB assesses executive functioning, attention, psychomotor speed and memory. It is comprised of paradigms commonly used in MCI/AD clinical trials, including verbal fluency (phonemic and category), psychomotor speed (symbol/digit substitution), and verbal learning and memory (with controlled attention and processing), as well as less frequently used measures to further probe the domain of executive functioning. These assessments will be used to characterize baseline cognitive status across several different performance domains before participants are randomized into one of 2 treatment sequences.

4.2.1.5 Planned Exploratory Biomarker Research

4.2.1.5.1 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.

In addition to studying variation across the human genome, apolipoprotein E (APOE) genotyping will specifically be investigated for its potential impact on response to treatment.

4.2.1.5.2 Exploratory Plasma Diagnostic Biomarkers for Alzheimer's Disease

The study will collect plasma for exploratory analysis of biomarkers indicating the presence of AD pathology (e.g. plasma beta-amyloid or plasma phospho-tau levels). These emerging biomarkers are not fully validated, but the rationale for inclusion of exploratory analysis in this study is to ascertain whether participants with biomarker data indicating the presence of AD pathology exhibit more robust changes in performance in OCL and other cognitive testing, and whether their responses to donepezil treatment are more pronounced than participants without biomarker evidence of AD pathology. This exploratory analysis will be

carried out on a post-hoc basis, using a plasma biomarker panel or panels that have not been specifically identified at the time of this protocol finalization, but are under investigation in other efforts and are anticipated to be available at the completion of this study.

4.2.1.6 Future Biomedical Research

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

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 FBR 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 FBR research are presented in Appendix 6.

4.2.2 Rationale for the Use of Placebo

Placebo will be used in this study to allow for an appropriate assessment of the cognitive platform's ability to detect treatment effect from donepezil 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 an 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

Donepezil is indicated for the treatment of dementia of the Alzheimer's type. In mild-to-moderate Alzheimer's patients, the maximum recommended dosage of donepezil in patients is 10 mg per day. A daily dose of 5 mg per day is indicated as a necessary titration step before administration of 10 mg to minimize side effects (typically gastrointestinal-related). The titration period in this study is 2 weeks, which is shorter than the recommended titration period in the donepezil label. The rationale for this shortened duration is to minimize participant time-in-study, and to further minimize the duration in treatment required to

observe a positive pro-cognitive pharmacodynamic effect. In MK-0000-318 (filed under IND 112,913), 30 participants with mild-to-moderate AD or MCI were titrated from 5-mg to 10-mg donepezil over 2 weeks. Of these, 4 participants randomized to receive donepezil discontinued participation due to an AE. The AEs leading to discontinuation were headache, insomnia, dizziness, and pruritus. In no cases were these AEs directly attributable to the accelerated titration approach in this study based on time of onset. Of note, in the pivotal donepezil studies, patients were titrated from 5 mg to 10 mg on Day 8 of treatment [U.S. Prescribing Information 2018]. Additional internal studies have similarly found that 2-week titration periods for donepezil are generally well-tolerated in the mild-to-moderate AD and MCI populations, further indicating that the safety and tolerability risk of this accelerated titration approach is low.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, 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.

5 STUDY POPULATION

Treatment-naïve male/female participants with MCI or mild AD between the ages of 55 and 85 years (inclusive) will be enrolled in this study. Inclusion of participants above the age of 80 years will need Sponsor’s approval before enrollment. Efforts will be made to enroll at least one-third of the participants meeting mild AD in this study.

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. Has an MMSE score between 18 and 28 (inclusive) at Screening (V1) and Baseline (V2), as confirmed by the rater training vendor. MMSE score at Screening and Baseline must be within 3 points of one another.

   Note: Due to the close timing between Visits 2 and 4, it is important to submit recordings and worksheets following the completion of the V2 MMSE to the rater training vendor to allow the rater training vendor to provide eligibility confirmation prior to completion of Visit 4. Participants whose scores are well within the specified range may proceed at the investigator's discretion. Participants with borderline MMSE scores (including potential differences between V1 and V2 MMSE ≥ 3 points of one another) should not proceed with randomization at Visit 4 until the eligibility confirmation from the rater training vendor is received.

2. Has a diagnosis of MCI or AD

   a. If the participant is diagnosed with MCI, the participant must:

      1. Have a history of subjective memory decline with gradual onset and slow progression for at least 1 year before Screening, that is either corroborated by an informant who knows the participant well or is documented in medical records

      2. Have a general cognitive function and activities of daily living sufficiently intact, based on clinical assessment, so as not to meet criteria for mild AD dementia based on NINCDS-ADRDA criteria

      3. Have a CDR scale score of 0.5, including a memory subscale score ≥ 0.5, as confirmed by the investigator (NOTE: If the Global CDR is 0.5, then the CDR sum of boxes [CDR-SB] score must be at least 2.0)

   b. If the participant is diagnosed with AD, the participant must:

      1. Have a history of cognitive and functional decline with gradual onset and slow progression for at least 1 year before Screening, that is either corroborated by an informant who knows the participant well or is documented in medical records

      2. Meet the criteria for a diagnosis of probable AD based on NINCDS-ADRDA criteria

      3. Have a CDR scale score of 1.0, as confirmed by the investigator

3. Has an MHIS score of ≤4.

4. Has an MRI scan at Screening to rule out non-AD conditions contributing to cognitive dysfunction. A scan that has been taken within 1 year of the Screening visit may be used, but either the scan or the diagnostic report must be made available for the investigator to independently assess.

Demographics

5. Is male or female, from 55 years to 85 years of age (inclusive), at the time of signing the informed consent. Inclusion of participants above the age of 80 years will need Sponsor's approval before enrollment.

Female Participants

6. A female participant is eligible to participate if:

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

Informed Consent

7. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study. The participant may also provide consent/assent for FBR. However, the participant may participate in the study without participating in FBR.

Additional Categories

The participant must:

8. Have a reliable and competent study partner/informant (e.g. spouse, family member, or other caregiver) who is knowledgeable of the participant's condition and progress and able to read, understand, and speak the designated language at the study site. The study partner/informant should understand the nature of the study and assist the participant with adherence to study requirements (e.g., study medication, visit schedules, evaluations). The study partner/informant must:

   a. Be willing to provide documented informed consent,

   b. Have contact with the participant at least three days a week for a minimum of six waking hours a week,

   c. Be willing to accompany the participant to the Screening Visit where the CDR scale is administered.

   d. Be willing to participate in assessments that require study partner/informant input (e.g., CDR scale).

9. Be willing to provide a blood sample for APOE genotyping. **Note**: Results from the APOE genotyping will not be used for determining eligibility.

10. Have results of clinical laboratory tests (hematology, chemistry, TSH, RPR, and urinalysis) within normal limits or clinically acceptable to the investigator at Screening.

11. Have results of a PE within normal limits or clinically acceptable to the investigator at Screening.

12. Have a history of academic achievement and/or employment sufficient to exclude intellectual disability as determined by the investigator.

13. Be able to speak, read, hear, and understand the language of the study staff and the ICF, and possess the ability to respond verbally to questions, follow instructions, and participate in study assessments based on the investigator's judgment (with legal representative input, as applicable).

14. Be able and willing to adhere to the study visit schedule.

15. Have visual acuity (with corrective lenses if needed), visual function (e.g. absence of color blindness), hearing (with supportive devices if needed), and gross and fine motor skills adequate to support study participation, based on participant’s medical history.

16. Be capable of performing the Cogstate battery assessments, as demonstrated at the Baseline/Familiarization Visit (Visit 2). Results of this assessment will be reported by Cogstate in the form of an Inclusion Report accessible via their electronic eSource Platform.

    Note: After battery completion, Cogstate will issue an auto-query for any test that fails their performance check during the screening period. The Sponsor should be consulted promptly if any Cogstate performance check auto-queries are issued at Visits 3 and 4. Participants should not be randomized at Visit 4 prior to this discussion with the Sponsor.

5.2 Exclusion Criteria

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

Medical Conditions

1. 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 assessment of suicidal ideation on the C-SSRS) in the *past 5 years* or suicidal behavior in *their lifetime.*

2. Has evidence of a clinically relevant neurological disorder other than AD at screening, including but not limited to: Parkinson's disease, frontotemporal dementia, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, progressive supranuclear palsy, dementia with Lewy bodies, other types of dementia, neurosyphilis or that led to persistent cognitive deficits, or has a history of seizures or epilepsy within the last 5 years before screening.

3. Has a known history of stroke that is clinically important in the investigator's opinion or has a diagnosis of possible, probable, or definite vascular dementia in accordance with the NINDS-AIREN criteria.

4. Has history of multiple episodes of head trauma, or head trauma resulting in protracted loss of consciousness, or serious infectious disease affecting the brain, within the prior 3-5 years.

5. Has evidence of a clinically relevant or unstable psychiatric disorder, based on DSM-5, including schizophrenia or other psychotic disorder, bipolar disorder, major depression, or delirium. **Note:** Major depression in remission for at least 6 months prior to screening is not exclusionary.

6. Has evidence of a current episode of major depression based on site investigator’s judgment. A score on the 15-item GDS of 5 or more requires an assessment by an appropriate health care professional to evaluate for the presence of major depression. **Note:** Participants with a score of 5 or more who are not diagnosed with major depression following such an assessment may be included in the study with Sponsor’s approval.

7. Has a recent or ongoing, uncontrolled, clinically significant medical condition within 2 months of the Screening visit (such as, but not limited to, diabetes, hypertension, thyroid or endocrine disease, congestive heart failure, angina, cardiac or GI disease, dialysis, or abnormal renal function) other than the condition being studied such that, in the judgment of the investigator, participation in the study would pose a significant medical risk to the participant. Controlled comorbid conditions (including diabetes, hypertension, heart disease, etc.) are not exclusionary if stable within 2 months of the Screening visit. All concomitant medications, supplements, or other substances should be kept as stable as medically possible during the study. **Note:** urinary tract infections at screening are not exclusionary if adequately treated (as documented by repeat urinalysis) prior to randomization.

8. Has a history of cancer (malignancy).

   Exceptions: (1) Adequately treated nonmelanomatous 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 Screening visit).

9. Has a relative contraindication to donepezil including sick sinus syndrome, first, second, or third degree heart block, bradycardia (with heart rate < 50 bpm at screening), active GI bleeding, Zollinger-Ellison syndrome, uncontrolled peptic ulcer disease, or uncontrolled asthma.

10. 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. **Exception:** Participants with selected allergies may be enrolled with Sponsor's approval.

11. Is positive for HBsAg, hepatitis C antibodies or HIV as confirmed by the central laboratory. **Exception**: Participants with a history of chronic hepatitis C infection with a documented cure and/or a positive serologic test for HCV with a negative HCV viral load may be included following Sponsor consultation.

12. Has clinically significant vitamin B12 or folate deficiency in the 6 months immediately before screening, or vitamin B12 or folate deficiency in addition to increased serum homocysteine and methylmalonic acid levels at screening as determined by central laboratory normal values. **Note:** Participants may be enrolled following initiation of B12 therapy for at least 1 month prior to randomization and with B12 level confirmed to be above lower limits of normal.

13. Has any clinically significant condition or situation, other than the condition being studied that, in the opinion of the investigator, would interfere with the study evaluations or optimal participation in the study.

Prior/Concomitant Therapy

14. Has ever received acetylcholinesterase inhibitors, memantine, or other symptomatic AD treatment. **Exception:** Inclusion of participants who last received such treatment 6 months ago (or earlier) prior to screening may be acceptable with Sponsor's approval.

15. Is unable to refrain from or anticipates the use of any of the medications listed in Table 2 throughout the duration of the study including the Poststudy visit. There may be certain medications that are permitted (see Exceptions noted in Table 2 and Section 6.5).

Table 2 Prohibited Medications that Require a Washout Period Prior to Completion of Visit 1 (Non-inclusive List)

Prohibited Medications, Supplements, and other Substances/Examples	Notes	Washout Period Prior to Completion of Visit 1[a]
AD Medications • Acetylcholinesterase inhibitors: galantamine, huperzine A, rivastigmine, tacrine, • memantine		6 months
Analgesics/Narcotics • codeine, dextromethorphan, hydromorphone, meperidine, morphine, oxycodone, pethidine hydrochloride, propoxyphene (Darvon) and its variations, combination products that contain a narcotic	**Exception:** if dosing is ≤ 2 doses/week (i.e. not regularly used) this is acceptable Prohibited 48 hrs before study visits	30 days or 5 half-lives, whichever is greater
Anesthetics (General)		3 months
Anticonvulsants/Mood Stabilizers • carbamazepine, levetiracetam, lithium, oxcarbazepine, phenytoin, valproic acid	**Exception:** use of pregabalin and gabapentin for neuropathic pain is acceptable	30 days or 5 half-lives, whichever is greater
Antidepressants (e.g. monoamine oxidase inhibitors [MAO], those with anticholinergic potency, or cognitive side effects: i.e. tricyclics) • amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, isocarboxazid, maprotiline, nortriptyline, phenelzine, protriptyline, tranylcypromine, trimipramine	**Exception:** selective serotonin reuptake inhibitor (SSRI) and serotonin–norepinephrine reuptake inhibitor (SNRI) antidepressants are permitted. Trazadone 150-200 mg for sleep is permitted.	30 days or 5 half-lives, whichever is greater
Antihistamines • chlorpheniramine, clemastine, cyproheptadine, diphenhydramine, hydroxyzine, pyrilamine	**Exception:** non-sedating antihistamines are allowed	30 days or 5 half-lives, whichever is greater
Antipsychotics/Neuroleptics • chlorpromazine, clozapine, fluphenazine, loxapine, methotrimeprazine, molindone, perphenazine, pimozide, promazine, thioridazine, thiothixene, trifluoperazine	**Exception:** asenapine, aripiprazole, lurasidone, olanzapine, quetiapine, risperidone, ziprasidone. Must be on stable dose 3 months prior to Screening Visit 1. Quetiapine is contraindicated 12 hours prior to cognitive testing.	30 days or 5 half-lives, whichever is greater
Antivertigo • meclizine, scopolamine		30 days or 5 half-lives, whichever is greater
Corticosteroids • oral, intravenous, or intramuscular • systemic glucocorticoids (dexamethasone)	**Exception:** topical and nasal use is acceptable	30 days or 5 half-lives, whichever is greater
CYP3A4 inhibitors (strong) • strong: boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole • other: grapefruit juice	**Exception:** topical use of these, if indicated, is acceptable	30 days or 5 half-lives, whichever is greater

Prohibited Medications, Supplements, and other Substances/Examples	Notes	Washout Period Prior to Completion of Visit 1[a]
CYP3A4 inducers (strong) • strong: avasimibe, barbiturates, carbamazepine, nevirapine, phenytoin, pioglitazone, primidone, rifabutin, rifapentine, St. John's Wort (hypericum) • systemic glucocorticoids (dexamethasone)	**Exception:** inhaled steroids are permitted	30 days or 5 half-lives, whichever is greater
Gastrointestinal • Antidiarrheal: diphenoxylate w/atropine • Antispasmodics: belladonna, clidinium, chlordiazepoxide, dicyclomine, hyoscyamine, propantheline, trimethobenzamide • Antiulcer: cimetidine, ranitidine		30 days or 5 half-lives, whichever is greater
Selected Herbal Supplements/Vitamins • Gingko biloba, ginseng, Huperzia serrata (Qian Ceng Ta), kava-kava, S-Adenosyl methionine (SAMe), tryptophan, valerian	**Exception:** Melatonin, Vitamin E, and Vitamin B12 are permitted. Consult Sponsor if questions on other herbal supplements/vitamins	30 days or 5 half-lives, whichever is greater
Hypnotics/Sedatives/ Benzodiazepines • chlordiazepoxide, clonazepam, diazepam, flurazepam, meprobamate, triazolam	**Exception:** Regular use (up to 3 times per week) of the following medications for sleep is acceptable if stable for at least 3 months prior to Screening Visit: trazodone, mirtazapine, zaleplon ≤ 5mg, zopiclone/eszopiclone ≤ 5 mg, zolpidem ≤ 5 mg, or lorazepam ≤ 1.0 mg. **However these medications may not be used for 24 hours before a cognitive assessment.** More frequent use may be allowed upon agreement from the site and Sponsor. For countries where these medications are not available, alternatives will be designated by the Sponsor	30 days or 5 half-lives, whichever is greater
Investigational Compounds		30 days or 5 half-lives, whichever is greater
Muscle Relaxants • cyclobenzaprine, dantrolene, methocarbamol, orphenadrine		30 days or 5 half-lives, whichever is greater
Ophthalmic • atropine		30 days or 5 half-lives, whichever is greater
Parkinsonism • amantadine, benztropine, biperiden, bromocriptine, levodopa, pergolide, rasagiline, selegiline, l-deprenyl/selegiline, trihexyphenidyl	**Exception:** pramipexole, ropinirole, and levodopa are allowed for treating restless leg syndrome	3 months
Stimulant medications • amphetamine, methylphenidate, atomoxetine, modafinil		30 days or 5 half-lives, whichever is greater

[a] Washout should occur for 5 half-lives or the minimum specified period whichever is longer to systemically eliminate the medication. It is recommended that sites that pre-screen potential participants review washout requirements in advance. Visit 1 maybe split to accommodate an extended washout period of 30 days; refer to Section 8.10.1 for details.

Prior/Concurrent Clinical Study Experience

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

Diagnostic Assessments

17. Has a known history of structural changes on screening MRI scan that are clinically important in the investigator's opinion, including signs indicative of vascular dementia, large infarct, lacunes in critical areas, space-occupying lesions, or extensive white matter disease.

Other Exclusions

18. Is unwilling or not eligible to undergo an MRI scan (if a prior MRI scan is not available).

19. Is under the age of legal consent.

20. Is pregnant, is attempting to become pregnant, or is nursing children.

21. Has a history of alcoholism or drug dependency/abuse within the last 5 years prior to the Screening visit.

22. 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.

23. 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.

24. Is a regular user of cannabis, any illicit drugs or has a history of drug (including alcohol) abuse within approximately 5 years. Participants must have a negative UDS prior to randomization. **Note:** A participant who is a recreational user of cannabis or other drugs within the past 2 years can be enrolled as long as recreational use does not meet the definition of drug abuse and participant agrees to refrain from substance use for duration of study participation.

25. Had major surgery (e.g. abdominal, thoracic, cardiac or orthopedic surgery, or any procedure requiring general anesthesia) within 3 months prior to the Screening visit that in the opinion of the investigator would interfere in the participant's ability to fully participate in the study.

26. Has undergone neuropsychological testing (including the MMSE) or cognitive remediation in the past 4 weeks.

27. 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.

28. 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

Participants should maintain their usual diet. Participants should 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 until the poststudy visit.

Fasting requirements for study procedures are limited to laboratory safety evaluations as specified in Appendix 2. Participants will fast from all food and drinks, except water, for at least 8 hours prior to the Screening and Poststudy visits.

Participants may administer trial medication with or without food, but trial medication should be taken with ~240 ml (8 oz) of water.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

Participants should refrain from consumption of caffeinated beverages or xanthine-containing products from 12 hours before the Screening and Poststudy visits.

Caffeinated beverages or xanthine-containing products should be limited to no more than 6 units per day (1 unit = 120 mg of caffeine). It is recommended that participants consume no more than their usual amounts of caffeine on the days of cognitive assessments, refrain from caffeine for at least 1 hour prior to the start of the Cogstate cognitive battery assessment and continue to refrain from caffeine until the completion of all cognitive assessments.

5.3.2.2 Alcohol Restrictions

Participants should refrain from consumption of alcohol 24 hours before the Screening and Poststudy visits. Participants should also refrain from consumption of alcohol for 12 hours before each clinic visit when cognitive assessments will be performed.

At all other times, alcohol consumption should be limited to no more than 1 alcoholic beverage 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

Participants will follow the smoking restrictions (and if applicable, the use of nicotine/nicotine-containing products) as defined by the CRU.

During the study, if the participant is a smoker, he/she should limit the number of cigarettes to 10 per day. Participants should not smoke within 30 minutes before the start of the Cogstate cognitive battery assessment.

5.3.3 Activity Restrictions

Participants should avoid unaccustomed strenuous physical activity (ie, weightlifting, running, bicycling, etc.) from the Screening visit until administration of the initial dose of study drug, throughout the study and until the Post Study visit.

Participants who are provided non-pharmacological treatments, such as day care, may continue these throughout the study. The frequency should not change unless medically indicated.

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 does not titrate successfully, 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.

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 (over-encapsulated donepezil and matching placebo) 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 participant. 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 3.

Table 3 Study Interventions

Arm Name	Arm Type	Intervention Name	Inter-vention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Admin-istration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
Active	Experimental	Donepezil hydrochloride	Drug	Capsule	5 mg	5 mg, 10 mg	Oral	QD dosing	Experimental	IMP	Provided centrally by Sponsor
Placebo	Placebo Comparator	Placebo	Drug	Capsule	0 mg	N/A	Oral	QD dosing	Placebo	IMP	Provided centrally by Sponsor
The classification of Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) in this table is based on guidance issued by the European Commission and applies to countries in the European Economic Area (EEA). Country differences with respect to the definition/classification of IMP/NIMP may exist. In these circumstances, local legislation is followed. In this protocol, the donepezil hydrochloride is over-encapsulated to match the placebo in order to maintain study blind.											

All supplies indicated in Table 3 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 to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is in Section 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.

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.

The sample allocation schedule is shown in Table 4.

Table 4 Sample Allocation Schedule

	Sample Size (N)	Run-In Period	Intervention Period
A (MCI)	16	Placebo	Donepezil
A (MCI)	8	Placebo	Placebo
B (Mild AD)	8	Placebo	Donepezil
B (Mild AD)	4	Placebo	Placebo

AD=Alzheimer's disease; MCI=mild cognitive impairment

The suggested sample size per treatment sequences and panel maybe adjusted by the sponsor based on enrollment metrics to ensure timely study completion. The allocation schedule will include additional allocation numbers per panel to enable flexibility to enroll more MCI (n >24) or more mild AD (n >12) participants as determined by the sponsor, but the total sample size of the study will remain approximately 36 participants. Participants may be replaced as needed to ensure that approximately 36 evaluable participants complete the study as described in Section 9.9.

6.3.2 Stratification

Intervention allocation/randomization will be stratified according to the following factors:

1. Disease status (MCI vs mild AD) as defined by CDR score at Screening

6.3.3 Blinding

During the placebo run-in period, a single-blinding technique will be used. The participant and his/her study partner will not know the study intervention they are administered; however, the investigator and Sponsor personnel or delegate(s) who are involved in study intervention administration or clinical evaluation of the participants will be aware of the intervention assignments to placebo. The placebo used during this period will be packaged identically to the drug supplies used in the subsequent treatment period during which a double-blinding technique with in-house blinding will be used. The donepezil is over-encapsulated to mimic the appearance of the placebo so that the blind is maintained. 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.

See Section 8.1.10 for a description of the method of unblinding a participant during the study should such action be warranted.

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.

- When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each subsequent visit. Compliance will be assessed by direct questioning and site review of the completed study intervention dosing diary as captured by the participant/study partner. In addition, compliance will be monitored via counting of returned capsules at selected site visits and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

- A record of the number of donepezil/placebo capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

- When participants are dosed at the site (for those who are domiciling overnight, as per Section 8.1.18), they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will also be recorded in the study intervention dosing diary (source documents).

6.5 Concomitant Therapy

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing study or during time periods specified by this protocol for that medication (Table 2 in Section 5.2). If there is a clinical indication for any medications specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Table 2 outlines specific restrictions for concomitant therapy during the course of the study; some exceptions are noted. For any concomitant medication not listed, the sponsor should be consulted. When medically possible, doses of concomitant medication, including medical food, should remain stable throughout the entire study.

In the event that a participant requires an extended washout period (ie, greater than 2 weeks) to accommodate discontinuation of a prohibited medication(s) or other therapy, an abbreviated Visit 1 may be performed (see Section 8.10.1). After the participant has completed the proper washout based on Table 2, the participant will return to complete the remaining Visit 1 procedures/assessments. Once the participant has fully completed Visit 1 and eligibility has been confirmed, the participant may proceed to Visit 2 per protocol.

Potential participants should not be withdrawn from medically necessary medications in order to participate in the study, but rather, these patients should be excluded from the study, due to their medical condition and the requirement for these therapies.

Paracetamol/acetaminophen or low dose non-steroidal anti-inflammatory drugs (ibuprofen/naproxen) may be used for minor ailments without prior consultation with the Sponsor.

In addition, the following concomitant medications/vaccinations are permitted:

1. All participants: Any immunizations/vaccinations

All participants: Any medication, excluding those listed in Table 2, intended for treatment of chronic, stable medical conditions (e.g. hypertension, vascular disease, diabetes), if participant has maintained compliance with a stable dosing regimen for at least 3 months prior to randomization

2. Female participants: hormonal replacement therapy is allowed, if on a stable dose initiated at least 3 months prior to randomization

3. All participants: AD medical foods/supplements (e.g., Axona®, Souvenaid®) is allowed if participant has been on a stable dosing regimen for at least three months prior to screening and plans to remain on the same regimen during the trial (unless a medically necessary change is needed)

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Sponsor Clinical Director should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Rescue Medications and Supportive Care

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

6.6 Dose Modification/Titration

During the double-blind intervention period, following 14 days of dosing, the dose of study medication will be increased from 5 mg donepezil (or placebo) to 10 mg donepezil (or placebo) at Visit 10. The decision to increase the dose will be made by the investigator based on his/her assessment of the participant's ability to tolerate the dose titration. If, in the opinion of the investigator, the participant is not suitable for dose titration, the sponsor should be consulted to determine the next step.

If the participant (or study partner on behalf of the participant) reports an initial tolerability issue after the dose titration step at Visit 10, the investigator will determine the participant's treatment plan and next steps (ie down-titrate to the original dose of 5 mg QD, continue with 10 mg QD (if applicable), or discontinue study intervention), with the decision to be mutually agreed upon by the investigator, the sponsor, and the study participant. For participants that were maintained at 5 mg donepezil (or placebo) due to tolerability issues, re-challenge to 10 mg may occur prior to Visit 13. However, participants who fail the mandatory first titration at 2 weeks of treatment will be excluded from the final primary analysis and may be replaced, at the discretion of the sponsor. However, data from participants failing the mandatory dose titration will be collected and may be included in additional post-hoc or exploratory analyses.

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 for the double-blind intervention period of this study]. 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.

See Section 8.1.10 for a description of the method of unblinding a participant during the study, should such action be warranted.

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 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 3 consecutive days within the double-blinded period or has 8 cumulative missed doses over the double-blinded period.

- 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.

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.

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, they shall not be allowed to restart study intervention.

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.

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.

The maximum amount of blood collected from each participant over the duration of the study will not exceed approximately 151 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 informed consent from each potential participant or their legally acceptable representative prior to participating in this clinical study or FBR. 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 documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised 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 or the participant's legally acceptable representative's dated signature.

Documented informed consent from each participant's study partner/informant (referred to as study partner informed consent) will also be obtained by the investigator or qualified designee.

Specifics about the study and the study population are to be included in the study informed consent form.

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 medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

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.

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 documented 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 30 days before starting the study.

When pre-screening potential participants, it is recommended that the site review the washout requirements of prohibited medications (Table 2) in order to allow sufficient time for washout prior to completion of Visit 1.

8.1.5.2 Concomitant Medications

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

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.

Any participant who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.10.1.

8.1.7 Assignment of Treatment/Randomization Number

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

A single participant cannot be assigned more than 1 treatment/randomization number.

As noted in Section 1.3, the treatment/randomization number is assigned to a participant at Visit 4 once it has been confirmed that the participant meets all eligibility criteria. To prepare for Visit 4, the site staff will contact the Sponsor for a treatment/randomization number to be used for this upcoming visit. Refer to the study operations manual for detailed procedures for requesting a treatment/randomization number.

8.1.8 Study Intervention Administration

Administration of study intervention will occur at home (or in-clinic if the participants are kept domiciled overnight for selected days) as described in Section 1.3 Schedule of Activities.

Participants will receive one bottle of study intervention at the Randomization Visit (V4) and at every two weeks at the third clinic visit for each testing period. Prior to dispensing a new bottle of study intervention, the previous bottle that was dispensed will be collected. Each bottle will contain enough study intervention to cover the duration of approximately 2 weeks (when the third clinic visit is scheduled within the permissible window per Section 1.3).

Each bottle dispensed at V4 will contain the placebo (matched to the over-encapsulated donepezil 5mg). Each bottle dispensed at V7 and thereafter will contain either the over-encapsulated donepezil 5 mg or placebo (matched to the over-encapsulated donepezil 5 mg). Participants will be instructed on how to administer study intervention by the site staff. Study intervention should begin on the evening of the visit when medication is dispensed.

While taking the study intervention at home, participants who vomit after dosing or miss a dose should be instructed to continue with the next scheduled dose.

8.1.8.1 Timing of Dose Administration

All study medication will be administered orally with water in the evening prior to retiring. Study intervention can be taken with or without food.

All doses should be taken at approximately the same time each night. Participants/study partners will record time of dosing in a study drug dosing diary. On days when study intervention is administered in-clinic at selected site(s), dose administration will be witnessed by the investigator and/or study staff.

If, in the opinion of the investigator, the timing of dose administration should be adjusted for an individual participant based on the participant's ability to tolerate the dose, the Sponsor Clinical Director must be consulted to determine next steps. In some cases, changes in timing of daily dosing may be permitted following Sponsor consultation.

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 and/or intervention. If a participant discontinues for any reason at any time during the course of the study and/or intervention, 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 8.4.1 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 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.

In the event that 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 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 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.

8.1.12 Rater Expectations and Training for Clinical and Cognitive Assessments

For this study, raters of clinical and/or cognitive assessments (MHIS [Section 8.13], MMSE [Section 8.1.14], CDR [Section 8.1.15], GDS [Section 8.1.16], C-SSRS [Section 8.3.6], Low Frequency Cognitive Battery [Sections 8.7.2, 8.7.3, and 8.7.4], Cogstate Battery [Section 8.7.1]) will be pre-qualified based on education and prior experience conducting protocol-specific or similar assessments, and experience working with patients with AD, MCI, or similar populations. Raters will undergo the applicable training and/or certification prior to conducting assessments in the study. Further, rater performance on some of these assessments will be carefully evaluated and monitored to ensure and maintain adequate reliability throughout the study. It is recommended that the same rater conducts the same assessment(s) throughout the study for a given participant and/or study partner, where feasible. Details will be specified in the MOA and in training materials provided by the rater training vendor or by Cogstate Ltd.

To ensure the continued quality of the assessments (MMSE, CDR, and other cognitive measures that constitute the Low Frequency Cognitive Battery), raters will be asked to audio record assessments at study visits. Some or all of these recordings will be reviewed by the rater training vendor, and raters will be provided feedback on the quality of their performance in order to help ensure data integrity. Based on this feedback, raters may be asked to consider changing their initially recorded scores if errors are identified. Routine rater meetings may be conducted to assess and maintain reliability for the duration of the study. Raters who do not perform adequately may be required to undergo additional remediation or may be replaced.

Recorded interviews will be secured using state of the art methods to ensure privacy. Recordings will only be reviewed by the rater training vendor for quality control purposes and will be destroyed in accordance with current retention requirements, unless local regulatory authorities or IRBs/ERCs have different requirements for storage.

8.1.13 Modified Hachinski Ischemia Scale

The MHIS, a tool to identify the possibility of a vascular etiology for the participant's cognitive impairment, will be completed by a qualified, trained rater. Additional detailed information concerning administration, scoring and documentation may also be provided by the rater training vendor and in the MOA.

8.1.14 Mini Mental State Examination

The paper version of the MMSE, a brief measure of cognition, will be administered to the participant and scored and recorded by a qualified, trained rater. Additional detailed information concerning administration, scoring and documentation may also be provided by the rater training vendor and in the MOA.

8.1.15 Clinical Dementia Rating Scale

The CDR, an assessment of global functioning, including performance in activities of daily living and cognition, will be administered to both the participant and the participant's study partner/informant and scored and recorded by a qualified, trained rater. Additional detailed information concerning administration, scoring and documentation may also be provided by the rater training vendor and in the MOA.

8.1.16 Geriatric Depression Scale – 15 Item

The 15-item GDS, a depression screening tool, will be administered to the participant and scored by a qualified, trained rater. Additional detailed information concerning administration, scoring and documentation may also be provided by the rater training vendor and in the MOA.

8.1.17 Magnetic Resonance Imaging

MRI scans should be performed during the screening period after all other inclusion and exclusion criteria has been met at Visit 1. Previous scans performed within 1 year of the documented ICF may be used in lieu of a screening scan provided the scans themselves or the report of the scan are made available to the investigator for review. The results of the MRI scan must be available, prior to Visit 2, to evaluate for study eligibility.

8.1.18 Domiciling (Optional)

For sites that have domiciling capability to keep participants overnight, the site may offer study participants the option to stay in the unit for the duration of the testing period in order to reduce the transportation burden associated with the high frequency clinic visits. The study partner is not required to stay overnight but may do so if requested by the study participant and the site can accommodate. If the participant is staying overnight at the CRU, then the 3 testing days should occur on consecutive days. At the discretion of the investigator, participants will report to the CRU the evening before the first scheduled testing day of each testing period and remain in the CRU until after the completion of study procedures on the

third testing day. Participants may be permitted to leave the unit, for emergency situations only, during the 3-day domiciling period at the discretion of the investigator after discussion with the Sponsor.

Study staff will also witness and administer the study medication and work with the participants in completing the dosing diary on the nights when the participants are in the CRU.

8.1.19 Participant and Study Partner Questionnaires (Optional)

At selected study visits as outlined in Section 1.3 SoA, the study participant and/or study partner will each complete a survey regarding their experience with the computerized cognitive battery testing and perspective on doing such assessments at home in a future clinical study.

8.1.20 History of Neuropsychological Assessments

The investigator or qualified designee will obtain a history of any neuropsychological testing that was performed within the past 6 months prior to Screening Visit 1 for each potential participant. Neuropsychological assessments include both paper/pencil cognitive measures as well as computerized cognitive batteries. The data to be recorded will include the name (and version, if known) of the individual measure or battery and the date when the assessment was performed. This historical information may support the characterization of the study population and the interpretation of the data from the cognitive assessments performed in this trial.

8.2 Efficacy 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/tissue to be drawn/collected over the course of the study (from Screening to Poststudy visits), including approximate blood/tissue volumes drawn/collected 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.

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 to 0.4 round down and 0.5 to 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 Neurological Examination

Targeted neurological examination will be conducted according to the procedures outlined in Appendix 9.

8.3.3 Vital Signs

8.3.3.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate, Respiratory Rate, and Blood Pressure)

Participants should be resting in a quiet setting without distractions in a semi-recumbent position for at least 10 minutes prior to having VS measurements obtained. Semi-recumbent VS will include HR, systolic and diastolic BP, respiratory rate and body temperature at timepoints indicated in the SoA. The correct size of the BP cuff and the correct positioning on the participants' arm is essential to increase the accuracy of BP measurements.

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.

8.3.4 Electrocardiograms

Single 12-lead ECG will be obtained during the screening period and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. A previous ECG performed within 3 months of the documented ICF may be used in lieu of a screening ECG provided the report is made available to the investigator for review.

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry before 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 position for at least 10 minutes before the ECG measurement.

The correction formula to be used for QTc is Fridericia.

8.3.5 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.

8.3.6 Suicidal Ideation and Behavior Monitoring

8.3.6.1 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 to be 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). Subsequent to that evaluation, only those participants whose suicidal ideation is considered by the evaluator to be passive, and 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; 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.

8.3.7 Photograph of Rash

Photographs of the rash are highly recommended to be taken immediately, along with any additional information that may assist the investigator to evaluate the skin reaction, skin eruption or rash occurrence in determining etiology and drug relationship.

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 participant provides documented informed consent, but before intervention 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, or a procedure.

From the time of intervention 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 5.

Table 5 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation (Randomized participants only)	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:
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
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: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in)	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential DILI - require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (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 (unless serious)
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 24 hours of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event

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

Care will be taken not to introduce bias when detecting AEs and/or SAEs 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

Although pregnancy and infant exposure during breastfeeding are not considered AEs and the study population includes WONCBP, if a pregnancy were to occur during the study (spontaneously reported to the investigator or their designee), it is reportable to the Sponsor.

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

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

Not applicable

8.4.7 Events of Clinical Interest

Selected serious and nonserious AEs 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, suicidal behavior

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 study 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 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 Donepezil

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

8.7 Pharmacodynamics

8.7.1 Computerized Cognitive Assessments

The Cogstate battery consists of the following tests presented to the participant in the order listed below. Details on how each test is performed will be provided in the Cogstate operation manual. All Cogstate Battery measures will be administered to participants by qualified, trained raters according to instructions and training provided by Cogstate Ltd. Raters should observe participants during the entire Cogstate Battery testing session and record notes as appropriate as the participant proceeds from one test to another. This will assist with addressing any Cogstate auto-queries that may arise after full battery completion.

The Cogstate Brief Battery

The CBB measures 4 core cognitive domains and consists of 4 modules:

- Detection Task (DET)- assesses psychomotor function and processing speed with a simple reaction time paradigm
- Identification Task (IDN)- assesses attention with a forced-choice reaction time paradigm
- One-Card Learning Test (OCL)- uses a pattern separation paradigm to assess visual memory
- One Back Test (ONB)- an n-back paradigm, where n = 1, is used to measure working memory

Additional Testing Modules

In addition to the Cognitive Brief Battery, the following tests from the Cogstate testing platform will be administered to explore the cognitive domains of complex attention, executive function, verbal/visual memory, and learning.

- The International Shopping List Test (ISLT [and ISRL])- uses a list-learning paradigm with a delayed recall component (ISRL) to assess verbal learning and memory. The participant will be asked to recall the words from the list approximately 15-20 minutes later (ISRL)
- The Modified Groton Maze Learning Test (GMLTM)- employs a maze-learning paradigm to assess executive functioning. The participants in this trial will be administered a modified version of the GMLT that is more appropriate for this trial population.

- The Continuous Paired Associate Learning Test (CPAL)- uses a paired-associates learning paradigm to measure visual learning and memory.

- The International Daily Symbol Substitution Test- Medicines (IDSSTM)- uses a symbol substitution paradigm to assess psychomotor processing speed.

- The Face Name Associative Memory Exam (FNAME) - employs a face/name associates learning paradigm to assess visual learning and memory.

8.7.2 Free and Cued Selective Reminding Test (FCSRT)

The FCSRT is a learning and memory measure in which participants are given categorical cues during acquisition to help maximize semantic encoding specificity and learning. As such, any deficits on recall are thought to reflect hippocampal-related memory impairment rather than inattention or other factors that may interfere with processing. In this study, both immediate and delayed recall will be evaluated. A brief paper/pencil task, it will be administered to the participant and scored by a qualified, trained rater according to instructions from the test manual and in the Manual of Assessments (MOA). Additional detailed information concerning administration, scoring and documentation may also be provided by the rater training vendor.

8.7.3 Wechsler Adult Intelligence Scale (WAIS-IV)-Coding

The Coding subtest of the WAIS-IV is a brief paper/pencil task assessing attention, psychomotor speed and visuomotor coordination. Coding will be administered to the participant and scored by a qualified, trained rater according to instructions from the test manual and in the MOA. Additional detailed information concerning administration, scoring and documentation may also be provided by the rater training vendor.

8.7.4 Tests from the Delis-Kaplan Executive Function System (D-KEFS)

Verbal Fluency

This protocol will include two tasks of the Verbal Fluency subtest. **Letter Fluency** measures phonemic fluency, while **Category Fluency** assesses semantic fluency and processing. Both are considered to be executive functioning tasks involving initiation, self-monitoring and processing speed. Also, both are brief paper/pencil measures that will be administered to the participant and scored by a qualified, trained rater according to instructions from the test manual and in the MOA. Additional detailed information concerning administration, scoring and documentation may also be provided by the rater training vendor.

Sorting

This task is comprised of two conditions, including Free Sorting and Sort Recognition. Taken together, they target a variety of executive functions, including problem-solving, concept formation, mental flexibility, creativity, and perseveration. A brief paper/pencil task,

it will be administered to the participant and scored by a qualified, trained rater according to instructions from the test manual and in the MOA. Additional detailed information concerning administration, scoring and documentation may also be provided by the rater training vendor.

Twenty Questions

Also an executive functioning measure, this test assesses problem-solving, abstraction, categorization, and incorporation of feedback. This brief paper/pencil measure that will be administered to the participant and scored by a qualified, trained rater according to instructions from the test manual and in the MOA. Additional detailed information concerning administration, scoring and documentation may also be provided by the rater training vendor.

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
- Blood for APOE Genotyping
- Blood for Exploratory Plasma Biomarkers for AD Diagnosis

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample will be drawn for APOE genotyping and for planned analysis of the association between genetic variants in DNA and drug response. If the IRB/IEC does not approve of the planned analysis of the association between DNA variation and drug response, or if there is a local law or regulation prohibiting the same, data analysis will be limited to APOE genotypes. Leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for FBR.

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

8.8.2 Exploratory Plasma Biomarkers for Alzheimer's Disease Diagnosis Sample Collection

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

8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for FBR, the following specimens will be obtained as part of FBR:

- Leftover DNA from Genetic Analysis and APOE Genotyping for future research
- Leftover main study plasma from donepezil PK stored for future research
- Leftover main study plasma from exploratory plasma biomarkers for AD diagnosis stored for future research

8.10 Visit Requirements

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

There are a total of 6 testing periods, each consisted of 3 clinic visits. It is recommended that the site schedules all study visits in advance when a participant is deemed eligible based on Visit 1 results. The 3 visits for each testing period (including the first testing cluster prior to Randomization) must be scheduled together, with the first 2 visits scheduled within 5 days of the last testing visit in that week. For example, Visits 2 and 3 are anchored by the date when Visit 4 is scheduled; they must be scheduled on any one of the 4 days prior to Visit 4 Randomization. Similarly, Visits 5 and 6 are anchored by the date when Visit 7 is scheduled; they must be scheduled on any one of the 4 days prior to Visit 7. Preferably, each cluster of 3 clinic visits should be scheduled within a single working week (which could include the following [not preceding] Saturday, if the clinic is open and staffed appropriately.)

An example would be as follows: a potential participant has completed screening at Visit 1 and is deemed eligible to move forward to Visit 2. The site would schedule this participant for Visit 2 at least 2 weeks from Visit 1, while ensuring that Visits 3 and 4 would occur within 4 days after Visit 2. At this time, the site would also schedule this participant for Visits 7, 10, 13, 16, and 19 (taken into account the permissible window for these “anchor” visits), while ensuring that Visits 5, 6, 8, 9, 11, 12, 14, 15, 17, and 18 will occur within the 4 days prior to the corresponding “anchor” visit.

Study Partner Participation

The study partner/informant is required to accompany the participant to the Screening Visit, in order to sign the study partner informed consent and to participate in the CDR assessment. The study partner is not required to accompany the participant to any other study visits, but if he/she is not able to do so, he/she should discuss alternative arrangements with the site (eg, participant transportation, return of study medication and dosing diary) and availability of the study partner to provide input by phone as needed (eg questions related to dosing information captured on dosing diary, optional questionnaire related to remote testing).

Every effort should be made to maintain the same study partner for the duration of the study. However, if the study partner is unable to continue with the study requirements, the study partner should discuss with the site whether a suitable replacement can be found. If a new study partner is identified, the new study partner will need to sign the study partner informed consent.

8.10.1 Screening (Visits 1-4)

The screening period ranges from approximately 3-7 weeks, including the initial testing period (Visits 2-4) occurring during the last week prior to randomization.

Screening Visit 1

Approximately 3-7 weeks prior to Visit 4 (when intervention allocation/randomization will occur), potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Screening Visit 1 should occur approximately 2 weeks prior to Visit 2 (Baseline/Familiarization Visit) but can be initiated earlier as permitted by the study visit window.

If a site wishes to split the Screening Visit 1 for a participant, the site may do so for the following reasons:

- Visit 1 may be split to decrease the burden of the participant/study partner due to the length of the visit.
- Visit 1 may be split in the event that a participant requires an extended washout period (ie, greater than 2 weeks) for prohibited medication(s) or other therapy, in accordance with Table 2; this is to help avoid the necessity to repeat any prior Visit 1 procedures assessed at the initial Visit 1.

If the site chooses to split Visit 1 for either of the reasons noted above, the site should ensure the comfort of study participants when considering the chronological order of procedures to be administered across the split screening visits. The site should also ensure that all prohibited medication(s) have been washed out as required per protocol prior to conducting the clinical and cognitive assessments (MMSE, CDR, MHIS, GDS, and C-SSRS).

The following is a recommendation of what procedures (non-inclusive) and the order they should be conducted at the initial portion of Visit 1:

- Obtain informed consent (Participant, Study Partner)
- Review medical history
- Preliminary review of inclusion/exclusion criteria

- Review of prior and concomitant medications
- Assignment of participant's screening number

The final portion of Visit 1 may include:

- All clinical and cognitive assessments (MMSE, CDR, MHIS, GDS, and C-SSRS)
- PE (including height/weight) and Neuro Exam
- Vitals, ECG, Labs
- MRI

The final portion of Visit 1 should be conducted preferably within 2 days of the initial portion of Visit 1, if splitting due to visit length. Participants required to washout of a prohibited medication will return to complete the final Visit 1 procedures once the washout has been completed. The local MRI screen (if a prior one is not available for review within 12 months prior to screening) should be the last procedure to be performed.

Assessments that are to be reviewed by the rater training vendor, such as the MMSE and CDR, **should be sent to the vendor as soon as possible (i.e., same day that the assessment was performed)** so specific eligibility criteria can be determined and the results can be sent back to the site in a timely manner. While quality review is conducted by the vendor for the MMSE and CDR, the MMSE inclusion criteria certificate is required as documentation for the site to confirm participant eligibility for Inclusion Criteria 1. At Visit 1, the MMSE and CDR should be considered as a bundle of screening assessments that should be administered at the same visit (i.e. sites should not administer MMSE without administering the CDR [or vice versa]). If MMSE and CDR were administered, then the audio-recordings and worksheets will need to be submitted to the rater training vendor regardless of scoring results or participant eligibility status. The sponsor/rater training vendor will query the site for missing audio-recording/worksheets should the vendor receive one measure but not the other.

Once a participant completes Visit 1 in its entirety and continues to meet eligibility, he/she may proceed to Visit 2 which should occur at least 2 weeks later. Participants with positive UDS due to prohibited medication(s) at Visit 1 must repeat the UDS. The repeat UDS may be performed at Visit 2 if needed, but the repeat UDS must be negative prior to V4 Randomization.

Participants may be rescreened after consultation with the Sponsor. Rescreening will be handled on a case-by-case basis and should include all screening procedures listed in the SoA, including consent review. Rescreen procedures cannot be conducted within the 4-day period prior to intervention allocation/randomization at Visit 4.

Baseline/Familiarization Visit and Testing Period 1 (Visits 2-4)

At least 2 weeks following Screening Visit 1, participants who have met the selection criteria thus far, will return to the CRU to undergo procedures to confirm eligibility at the Baseline/Familiarization Visit (Visit 2). This will be the first of 3 cognitive testing days for the first testing period in this study. This first testing period is to familiarize the participants with the Cogstate battery as well as the high frequency testing schedule, and to ensure potential participants are able to complete the computerized cognitive assessments.

At this visit, the CBB (which consists of the DET, IDN, OCL, ONB subtests) will be administered 2 times separated by a rest period of approximately 15 minutes.

During this first testing period and throughout the study, participants will report to the CRU at approximately the same time in the morning (+/- 2 hours) for each testing visit. Cogstate assessments should be performed before any other procedures planned for a study visit (See Section 1.3 for a list of procedures). See Table 6 in Section 8.10.2 for recommended timings with built-in testing breaks on the longer testing visits.

Participants who have met all selection criteria at Randomization Visit 4 will be assigned randomization numbers and dispensed medication to take home, with instructions to take the first dose later that evening before retiring for bed. Study intervention dosing diary will be given to the participant with instructions to record dosing information nightly.

8.10.2 Treatment Period (Visits 5-19)

The treatment period consists of a single-blind placebo run-in (Visits 5-7), followed by a double-blind intervention period (Visits 8-19). Participants/study partners should not be informed of when they are transitioning into a different study period (e.g. run-in vs double-blind intervention).

Placebo Run In: Testing Period 2 (Visits 5-7)

After completion of Testing Period 1 (at Visit 4), randomized participants will enter the placebo run-in period of approximately 14 days. Participants will return to the CRU at approximately 2 weeks after the first testing period for Testing Period 2 consisting of 3 clinic visits as outlined in Section 1.3. At the third testing visit of this testing period, participants will return their medication bottles (containing placebo). At the end of this visit, the participants will be sent home with new medication bottles (containing randomized treatment of donepezil or placebo) with instructions to take the first dose later that evening and continue taking one capsule nightly. Participants will be instructed to record dosing information in the dosing diary.

Double-Blind Intervention: Testing Periods 3, 4, 5, and 6 (Visits 8-19)

After completion of Testing Period 2 (in the morning of Visit 7), participants will enter the Double-Blind Intervention period of approximately 8 weeks (with the commencement of

dosing later that same evening). Because participants will be dosed with donepezil 5 mg (or placebo) during the first 2 weeks of this intervention period before titrating up to 10 mg (or placebo), it is important that the third testing visit of Testing Period 3 (Visit 10) does not occur earlier than Day 15 when participants will exchange for new medication bottles with new instructions to take 2 capsules nightly for the remainder of the study.

After completion of Visit 10 and for the remaining 6 weeks of this double-blind treatment period, participants will return to the CRU at approximately 2-week intervals for 3 additional testing periods (Testing Periods 4, 5, and 6, consisting of 3 visits each) as outlined in Section 1.3 SoA. At the third visit of each testing period, participants will continue to exchange their medication bottle for a new bottle, with the exception of Visit 19 which is the End of Treatment visit. Participants should bring their study drug dosing diary when return to the clinic for medication compliance checks.

During the placebo run-in and double-blind intervention periods, participants will report to the CRU at approximately the same time in the morning (+/- 2 hours) for each testing visit, consistent with the schedule set forth during the first testing period. Cogstate assessments should be performed before any other procedures planned for a study visit (See Section 1.3 for a list of procedures).

Cognitive assessments should be done in a secluded room/area, free from distractions. The rater should see to the participant's needs, such as drink or restroom, prior to starting as to minimize interruptions. Breaks are allowed but should be appropriate and not excessive. Table 6 provides a sketch of the procedures and recommended timings for a participant on the longer testing visits at Visit 3 (Pre-Treatment) and at Visit 18 (End of Treatment).

Table 6 Recommended Order and Timing of Procedures at Visits 3 and 18

Procedure	**V3**	**V18**
Assess concomitant medication use and AE(s)	X	X
Cogstate Battery	X	X
15-min Break[a]	X	X
FCSRT[b]	X	X
WAIS-IV Coding	X	X
Sorting (D-KEFS)	X	X
15-min Break[a]	X	X
Verbal Fluency Test (D-KEFS)[c]	X	X
Twenty Questions (D-KEFS)	X	X

AE=adverse event; D-KEFS = Delis-Kaplan Executive Function System; FCSRT = Free and Cued Selective Reminding Test; WAIS = Wechsler Adult Intelligence Scale

[a] Short break to stretch or visit restroom facility; participant should not be given reading materials or become engrossed in other activities during this time.

[b] No other cognitive assessments can be performed during the 20-30 min interval between Trial 3 of Free and Cued Recall and the start of Delayed Recalled portion of the FCSRT. The participant will be given another short break during this time.

[c] For the Verbal Fluency Test, only the letter fluency and category fluency tasks will be administered.

Note that the LFCB assessments may be split across 2 days (i.e. Visits 3-4; and Visits 18-19) to decrease participant burden. The rater should ensure consistency in the administration of the LFCB during the course of the study. If the screening/pre-treatment LFCB was performed over 2 days for an individual participant at Visits 3-4, then the LFCB scheduled for the later timepoint (i.e. Visit 18) should also be consistently split across 2 days (i.e. Visits 18-19). Table 7 is a recommendation of how the LFCB assessments should be conducted across 2 study visits.

Table 7 Recommended Order and Timing of Procedures at Visits 3-4 and 18-19 if Splitting Visits

	Visit 3 Split Visit[a]		Visit 18 Split Visit[a]	
Procedure	**V3**	**V4**	**V18**	**V19**
Assess concomitant medication use and AE(s)[b]	X	X	X	X
Review Study Intervention Dosing Diary			X	X
Cogstate Battery	X	X	X	X
15-min Break[c]	X	X	X	X
FCSRT[d]	X		X	
WAIS-IV Coding	X		X	
Sorting (D-KEFS)	X		X	
Verbal Fluency Test (D-KEFS)[e]		X		X
Twenty Questions (D-KEFS)		X		X
Blood Collections[f]		X		X

AE=adverse event; D-KEFS = Delis-Kaplan Executive Function System; FCSRT = Free and Cued Selective Reminding Test; WAIS = Wechsler Adult Intelligence Scale

[a] Procedures for Visit 3 and Visit 18 split across 2 days, with some procedures conducted at Visit 4 and Visit 19, respectively.

[b] Includes C-SSRS (at selected timepoints per Section 1.3 SoA)

[c] Short break to stretch or visit restroom facility; participant should not be given reading materials or become engrossed in other activities during this time.

[d] No other cognitive assessments can be performed during the 20-30 min interval between Trial 3 of Free and Cued Recall and the start of Delayed Recalled portion of the FCSRT. The participant will be given another short break during this time.

[e] For the Verbal Fluency Test, only the letter fluency and category fluency tasks will be administered.

[f] Blood for Genotyping/PK/Biomarkers (if applicable as per Section 1.3 SoA)

8.10.3 Poststudy (Visit 20)

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.

8.10.4 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the computerized cognitive assessment with the CBB is the critical procedure and should be administered at close to the exact time point as possible, at approximately 2-week intervals as outlined in Section 1.3. The scheduling of the visits for the third testing period (Visits 8-10) must coincide with the schedule for the planned up-titration when new medication is dispensed with new dosing instruction (at Visit 10).

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 Collections as outlined in Table 8

Table 8 Pharmacokinetic (Blood) Collection Windows

PK Collection	PK Collection Window
Visits 10, 13, 19 (per Section 1.3 SoA)	Within the 4 days prior to the scheduled visit (to coincide with one of the testing days)

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

This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Modifications to the 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.

If it is determined that incomplete or aberrant data has been captured during the CBB assessments at any study visit, the participant may be asked to repeat the assessment. The evaluation to determine whether the assessment is to be repeated will be done on an individual basis per participant, and the decision will be reached by mutual agreement of the Sponsor and investigator.

Up to additional 50 mL of blood may be drawn for safety 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 (Appendix 8).

The timing of procedures for assessment of safety procedures (eg, vital signs, 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

The statistical analysis of the data obtained from this study will be conducted by the Experimental Medicine Statistics Department in collaboration with the Translational Medicine Departments of the Sponsor. If, after the study has begun, changes are made to the statistical analysis plan stated below, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the Results Memo for this study.

9.1 Statistical Analysis Plan Summary

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

To assess the primary hypothesis, the repeated measurements associated with proportion of correct response in the OCL task at each of Weeks -1, 2, 4, 6 and 8 will be averaged by each participant. Intermittent missing repeated measures within a time point (e.g., Week 2) will not be imputed and data will be averaged as available. Observations with integrity failures will be excluded from analysis and will not be imputed. Change from placebo run-in period (i.e. Week -1) in the average correct response of OCL measurements will be estimated using a linear mixed effects model containing fixed effects for Week, proportion of correct response in the OCL measurement at baseline (placebo run-in period), Treatment (donepezil/placebo) and Week by Treatment interaction with an unstructured covariance matrix which will account for missing data under a missing at random assumption. Least square variances will be estimated for change from placebo run-in period by treatment group (donepezil/placebo) and Week 8 using above mentioned linear mixed models. The posterior distribution of the variances will be estimated by generating 10,000 independent draws from non-informative Inverse Gamma prior for both treatment groups. Conditioned on each variance, difference of average correct response rate of OCL task from placebo run-in period will be generated from a Normal distribution with mean equal to the estimated least square mean estimate for both groups at Week 8. The posterior probability of true mean difference between donepezil and placebo group at Week 8 relative to Week -1 is greater than 2 percentage points will be derived from the posterior distribution. A posterior probability that is > 55% will satisfy the primary hypothesis.

Power: The probability to satisfy the primary hypothesis under varying true mean change in donepezil population is shown in Table 9. With 36 participants (24 in donepezil and 12 in placebo), there is ~ 64% power to satisfy the criteria (posterior probability >55%) for the primary hypothesis if the true mean change from placebo run-in period is 3 percent points for donepezil group, assuming there no change in placebo group. For the donepezil group, if the true mean change is 4 percentage points then the corresponding power increases to 78%.

Table 9 Power Primary Hypothesis

True Mean Change in Donepezil	Prob (Post prob. of difference of true mean change from placebo run-in between the donepezil and placebo groups > 0.02) >		
	P = 60%	P = 55%	P = 50%
2.0%	0.407	0.456	0.509
2.5%	0.483	0.532	0.582
3.0%	0.576	0.635	0.684
3.5%	0.669	0.713	0.754
4.0%	0.741	0.778	0.816

9.2 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be the responsibility of the Experimental Medicine Statistics department of the Sponsor.

9.3 Hypotheses/Estimation

Primary:

After 8 weeks of daily treatment, the change from placebo run-in period (Week -1) in average proportion of correct responses in the One Card Learning (OCL) task (a task of visual learning) in participants receiving donepezil compared with participants receiving placebo will be ≥2 percentage points.

Secondary:

- The overall standard deviation associated with the change from placebo run-in period in average OCL repeated measurements (arcsine square root transformed) after 8 weeks of donepezil treatment is ≤ 0.1.
- After 8 weeks of daily treatment in subjects receiving donepezil, the proportion of correct responses in the OCL task will improve relative to performance on the placebo run-in period by a clinically meaningful (>2 percentage points) degree of change.

9.4 Analysis Endpoints

Primary Endpoint:

Proportion of correct responses in the One Card Learning (OCL) task (a task of visual learning) at Weeks -1, 2, 4, 6 and 8.

Exploratory Endpoints:

- Other measures of Cogstate test battery (Detection (DET), Identification (IDN), One Back (ONB), International Shopping List Test (ISLT), Modified Groton Maze Learning Test (GMLTM), Continuous Paired Associate Learning (CPAL), International Daily Symbol Substitution Test -Medicines (IDSSTM), International Shopping List Test - Delayed Recall (ISRL)) at Weeks -1, 2, 4, 6 and 8.
- Measures related to the Face-Name Associative Memory Exam (FNAME).
- Measures related to Free and Cued Selective Reminding Test at Weeks -3 and 8.
- Measures related to Wechsler Adult Intelligence Scale (WAIS-IV) Coding at Weeks -3 and 8.
- Measures related of D-KEFS (Sorting, Verbal Fluency, Category Fluency, Twenty Questions) at Weeks -3 and 8.
- Measures related to beta-amyloid and phosphor-tau proteins.
- Measures related to PK data.
- Measures that capture the concept of operational feasibility of frequent site-based administration of cognitive function testing in participants with MCI/mild AD.
- Measures participants' and study partner/informants' perception and comfort with the use of at-home device (e.g. tablet/computer) in future studies.

9.5 Analysis Populations

The Full Analysis Set for each endpoint will be comprised of all participants who receive study medication and yield at least one valid measurement for that endpoint. Data from participants who discontinue donepezil therapy will be considered missing at time points after therapy discontinuation.

9.6 Statistical Methods

The primary hypothesis is related to proportion of correct response in the OCL task associated with change from placebo run-in period (Week -1) at Week 8 for donepezil group compared with placebo group. To assess the primary hypothesis, the repeated measurements

associated with proportion of correct response in the OCL task at each of Weeks -1, 2, 4, 6 and 8 will be averaged by each participant. Intermittent missing repeated measures within a time point (e.g., Week 2) will not be imputed and data will be averaged as available. Observations with integrity failures will be excluded from analysis and will not be imputed. The amount and patterns of missing data will be summarized. Change from placebo run-in period in the average correct response of OCL measurements will be estimated using a linear mixed effects model containing fixed effects for Week, proportion of correct response in the OCL measurement at baseline (placebo run-in period), Treatment (donepezil/placebo) and Week by Treatment interaction with an unstructured covariance matrix which will account for missing data under a missing at random assumption. Least square variances will be estimated for change from placebo run-in period by treatment group (donepezil/placebo) and Week 8 using above mentioned linear mixed models. The posterior distribution of the variances will be estimated by generating 10,000 independent draws from non-informative Inverse Gamma prior for both treatment groups. Conditioned on each variance, difference of average correct response rate of OCL task from placebo run-in period will be generated from a Normal distribution with mean equal to the estimated least square mean estimate for both groups at Week 8. The posterior probability of true mean difference between donepezil and placebo group at Week 8 relative to Week -1 is greater than 2 percentage points will be derived from the posterior distribution. We can rewrite the model as following

$$\sigma^2 \sim Inverse\ Gamma\ (\alpha, \beta), where\ \alpha = \beta = 0.0001$$

$$\sigma^2_{trt}|y_{iw} \propto Inverse\ Gamma\left(\alpha + \frac{n_{trt}}{2}, \beta + \frac{n_{trt}}{2}\ S^2_{trt}\right), where\ trt = \text{donepezil, placebo}$$

$$y_i|. \sim \text{Normal}(\hat{\mu}_{trt}, \sigma^2_{trt}|.), \text{where i} = \begin{cases} 1, \ldots, 24\ when\ trt = donepezil \\ 1, \ldots, 12\ \ when\ trt = placebo \end{cases}$$

The above equations will be repeated for 10,000 times to estimate

$$Prob\left((\bar{y}_{donepezil} - \bar{y}_{placebo}) > 0.02\right)$$

A posterior probability that is > 55% will satisfy the primary hypothesis.

To assess the secondary hypothesis related to the true standard deviation (SD) associated with the change from placebo run-in period in average OCL measurements, the individual OCL measurements will first be transformed using the arcsine square root function. For each patient, the 3 transformed OCL measurements at each of Weeks -1, 2, 4, 6 and 8, will be averaged. Intermittent missing repeated measures within a time point (e.g., Week 2) will not be imputed and data will be averaged as available. The amount and patterns of missing data will be summarized. The variance/covariance matrix of the average transformed OCL measurements will be estimated using a linear mixed effects model containing fixed effects for Week, Treatment (donepezil/placebo) and Week by Treatment interaction. An unstructured covariance matrix will be estimated that principally accounts for missing data under missing at random assumption. The Kenward & Roger's approximation will be used to compute the appropriate model-based degrees of freedom. Utilizing a non-informative prior,

the posterior distribution of the true variance/covariance matrix will be estimated by generating 5000 independent draws from an inverse Wishart distribution, with the model based degrees of freedom and matrix S, where S is the model-based degrees of freedom times the model estimated variance/covariance matrix. For each generated true variance/covariance matrix, a plausible true SD of the change from baseline in average OCL measurements at Week 8 relative to Week -1 will be calculated. The posterior probability that the true SD of the change from baseline in average OCL measurements at Week 8 relative to Week -1 is ≤ 0.1 will be derived from the posterior distribution. A posterior probability that is > 70% will satisfy the secondary hypothesis.

To assess the secondary hypothesis related to the effect of donepezil, least square variance will be estimated for change from placebo run-in period at Week 8 for donepezil group using above mentioned linear mixed models. The posterior distribution of the variance will be estimated by generating 10,000 independent draws from non-informative Inverse Gamma prior. That is, conditioned on variance, difference of average correct response rate of OCL task from placebo run-in period will be generated from a Normal distribution with mean equal to the estimated least square mean estimate for donepezil group at Week 8. The posterior probability that the true mean difference is greater than 2 percentage points will be summarized.

9.7 Interim Analyses

No interim analyses are planned for this study.

9.8 Multiplicity

Since there is only one primary hypothesis, no multiplicity adjustment will be employed.

9.9 Sample Size and Power Calculations

The probability to satisfy the primary hypothesis under varying true mean change in donepezil population is shown in Table 10. There are 24 participants in the donepezil group and 12 participants in the placebo group. In the placebo group, true mean change from placebo run-in period is assumed to be zero with SD of 0.06. In the donepezil group, the SD of the change from placebo run-in is 0.07. SD in both groups are consistent with estimated SD from MK-0000-318 study. With 36 participants (24 in donepezil and 12 in placebo), there is ~ 64% power to satisfy the primary hypothesis if the true mean change from placebo run-in period is 3 percentage points for donepezil group, assuming there no change in placebo group. For donepezil group, if the true mean change is 4 percentage points then the corresponding power increases to 78% as displayed in the last row of Table 10.

Table 10 Power associated with Primary Hypothesis

True Mean Change in Donepezil	Prob (Post prob. of difference of true mean change from placebo run-in between the donepezil and placebo groups > 0.02) >		
	P = 60%	P = 55%	P = 50%
2.0%	0.407	0.456	0.509
2.5%	0.483	0.532	0.582
3.0%	0.576	0.635	0.684
3.5%	0.669	0.713	0.754
4.0%	0.741	0.778	0.816

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 LLC, Rahway, NJ, USA (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 laws and 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 and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. 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 potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are 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, as well as all applicable data protection rights. 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 Harmonisation 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 participants' documented informed consent, 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 11 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- 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 11 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	BUN	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the ULN)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Glucose (fasting)	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	• FSH (as needed in WONCBP only) • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serology (HIV antibody, HBsAg, and hepatitis C virus antibody, RPR) • Vitamin B12, Folate (Homocysteine and MMA are required in case of Vitamin B12 and/or folate deficiency) • TSH (and T3/T4, if TSH is abnormal)			

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; MMA=Methylmalonic Acid; RBC=red blood cell; RPR=Rapid Plasma Reagin; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; TSH=Thyroid Stimulating Hormone; ULN=upper limit of normal; WONCBP=women of nonchildbearing potential

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, medical device, combination product, 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."

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:

a. **Results in death**

b. **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.

c. **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.

d. **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.

e. **Is a congenital anomaly/birth defect**

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

f. **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

- 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: Medical Device and Drug-device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

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.

10.6 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 participants' 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 sex, 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 Harmonisation [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

Not applicable.

10.8 Appendix 8: Blood Volume Table

	Screen-ing	Random-ization (Visit 4)	Treatment Period (Visits 10, 13, 19)	Poststudy (Visit 20)	Total Collections	mL Per Collection	Total mL/ Test
Chemistry (including TSH, Vitamin B12, & FSH at Screening)	1			1	2	8	16
Hematology	1			1	2	3	6
Folate, MMA, RPR	1				1	8	8
Homocysteine	1				1	3	3
HIV/Hepatitis Screen	1				1	6	6
Blood for Plasma Donepezil Assay			3		3	3	9
Blood for Exploratory Plasma Biomarkers for AD Diagnosis		1	1		2	20	40
Blood for APOE genotyping		1			1	4	4
Blood for Planned Genetic Analysis		1			1	8.5	8.5
Total Blood Volume for Participant							100.5
If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary (including the need for a repeat FSH to confirm postmenopausal status if duration of amenorrhea is less than 12 months), additional blood (up to 50 mL) may be obtained.							

10.9 Appendix 9: Targeted Neurological Examination

Note to the investigator: If abnormalities are observed in the Targeted Neurological Exams, the Investigator should do additional examinations as needed based on his or her medical judgment to determine participant eligibility in the study.

MODULE 1 – MENTAL STATUS EXAMINATION

(Note this module is covered by MMSE)

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 - COORDINATION AND GAIT

D. Gait

1. 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.

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
AE	adverse event
APOE	Apolipoprotein E
AR	adverse reaction
BMI	body mass index
BP	blood pressure
CBB	Cogstate Brief Battery
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating- Sum of Boxes
CG	Cockcroft-Gault
CL	clearance
CNS	central nervous system
CPAL	Continuous Paired Associate Learning (Cogstate Test)
CR	complete response
CRF	Case Report Form
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical Study Report
D-KEFS	Delis-Kaplan Executive Function System
DET	Detection (Cogstate Test)
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
EMA	European Medicines Agency
FBR	Future Biomedical Research
FCSRT	Free and Cued Selective Reminding Test
FDAAA	Food and Drug Administration Amendments Act
FNAME	Face Name Associative Memory Exam
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
GI	gastrointestinal
GMLTM	Modified Groton Maze Learning Test (Cogstate Test)
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ID	Identification
IDN	Identification (Cogstate Test)

Abbreviation	Expanded Term
IDSSTM	International Daily Symbol Substitution Test- Medicines (Cogstate Test)
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
ISLT	International Shopping List Test (Cogstate Test)
ISRL	International Shopping List Test – Delayed Recall (Cogstate Test)
MedDRA	Medical Dictionary for Regulatory Activities
MCI	Mild cognitive impairment
MHIS	Modified Hachinski Ischemia Scale
MMSE	Mini Mental State Examination
MOA	Manual of Assessments
MRI	magnetic resonance imaging
mRNA	messenger RNA
NDA	New Drug Application
NINCDS-ADRDA	National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association
NINDS-AIREN	National Institute of Neurological Disorders and the Stroke Association Internationale pour la Recherche l'Enseignement en Neurosciences
NTB	Neuropsychological Test Battery
OCL	One-Card Learning (Cogstate Test)
ONB	One Back (Cogstate Test)
OTC	over-the-counter
PCL	protocol clarification letter
PE	physical examination
PK	pharmacokinetic
po	orally
PP	per-protocol
qd	Once per day
RNA	ribonucleic acid
RPR	rapid plasma reagin
SAE	serious adverse event
SAP	Statistical Analysis Plan
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
Tmax	Time to maximum plasma concentration
t1/2	half life
TSH	thyroid stimulating hormone
UDS	urine drug screen
V	volume of distribution
VS	vital sign
WAIS	Wechsler Adult Intelligence Scale
WBC	white blood cell

11 REFERENCES

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[U.S. Prescribing Information 2018]	U.S. Prescribing Information: ARICEPT (donepezil hydrochloride) tablets, for oral use; ARICEPT ODT (donepezil hydrochloride) orally disintegrating tablets: Dec 2018.	[05L9XJ]