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261-00

A Study to Assess the Feasibility, Sensitivity and Specificity of CSF Collection for Assays of Alzheimer's Disease Biomarkers

Product: Non-Product
Protocol/Amendment No.: 261-00

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TITLE:

A Study to Assess the Feasibility, Sensitivity and Specificity of CSF Collection for Assays of Alzheimer's Disease Biomarkers

INVESTIGATOR:

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INSTITUTIONAL REVIEW BOARD/ETHICS REVIEW COMMITTEE:

PROTOCOL

A Study to Assess the Feasibility, Sensitivity and Specificity of CSF Collection for Assays of Alzheimer's Disease Biomarkers

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1. SUMMARY

1.1 TITLE

A Study to Assess the Feasibility, Sensitivity and Specificity of CSF Collection for Assays of Alzheimer's Disease Biomarkers

1.2 INDICATION

Not Applicable

1.3 SUMMARY OF RATIONALE

Alzheimer's disease (AD) is the leading cause of dementia, and there is no effective disease-modifying therapy at present. Clinical trials for AD have been hampered by slow clinical progression, clinical misdiagnosis, and lack of predictive biomarkers. Recent studies suggest that analysis of cerebrospinal fluid (CSF), specifically, levels of the proteins tau and $A\beta_{1-42}$, can improve subject selection for clinical studies. Considering the CSF tau/$A\beta_{1-42}$ ratio in conjunction with clinical exam data improves the likelihood that a given trial subject actually has AD and not another dementing disorder. Thus, use of CSF biomarkers can improve the sensitivity and power of clinical trials in AD, particularly in identifying those patients with prodromal AD. Merck Research Laboratory (MRL) scientists have recently determined that $A\beta_{1-42}$ can adhere to plastic and that addition of detergent to sample collection tube can improve recovery of $A\beta_{1-42}$. Thus, the cutoff criteria to discriminate between AD subject and healthy elderly need to be determined with detergent present in collection tubes. In an ongoing study, CSF tau/$A\beta_{1-42}$ ratios are being determined for cohorts of HE and AD patients, using the MRL assays. The cutoff for distinguishing HE and AD emanating from this ongoing study will be applied in to the current study.

The goals of the current study are: 1) to determine the logistical feasibility of CSF sample collection from multiple sites to aid in patient selection, and 2) to confirm the specificity and sensitivity of the MRL CSF assay in distinguishing healthy elderly subjects from AD patients, using a ratio cutoff value generated from a separate study of different AD and healthy elderly subjects.

1.4 SUMMARY OF STUDY DESIGN

This study is a multi-center trial to assess the tau/$A\beta_{1-42}$ ratio in CSF from healthy elderly and mild to moderate AD patients. Ratio ranges between the two populations as well as variability between sites will be assessed. The study has no treatment and there is no randomization; patients that meet the inclusion/exclusion criteria specific to their target population will be allocated to receive a lumbar puncture (LP). The operational feasibility of obtaining and analyzing tau/$A\beta_{1-42}$ ratio results within a short period of time, approximately 1-2 weeks, will also be assessed.

The study will consist of 2 visits: a screening visit, the treatment visit to collect CSF via lumbar puncture and a safety follow up phone call. Patients will remain in the clinic for approximately 4 hours after the LP or until the investigator feels it is safe for them to leave.

1.5 SAMPLE

Male and female healthy elderly (HE) subjects and mild to moderate Alzheimer's Disease (m/m AD) patients aged 60-80, inclusive, will be enrolled. There will be approximately 11 sites; each site will be expected to have approximately 5 HE subjects and 5 m/m AD patients complete the study.

1.6 DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN

Not applicable

1.7 STUDY FLOW CHART

	Visit 1[a] Screening Visit	Visit 2 Treatment Visit	Visit 3 Safety Follow Up[i]
Informed Consent	X		
Informed Consent for Future Biomedical Research[b]	X		
Review of Inclusion/Exclusion criteria	X		
Review of prior and concomitant medications	X	X	
Medical history	X		
Informant Interview	X		
Physical and Neurological examination	X		
12-lead ECG	X		
Height and Weight	X		
Vital Signs[c]	X	X	
Laboratory Safety Tests (Appendix 6.1 and 6.2)	X		
Urine collection for biomarker analysis[f]	X	X	
Mini-Mental State Exam (See Study Operations Manual)	X		
Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB) (See Study Operations Manual)	X		
ADAS Cog[d] (See Study Operations Manual)	X		
ADCS-ADL[d] (See Study Operations Manual)	X		
Modified Hachinski Ischemia Score (See Study Operations Manual)	X		
Structural MRI[h]	X		
Diagnosis and Narrative Summary (AD only)[e] (See Study Operations Manual)	X		
Assign Allocation number		X	
Blood for Future Biomedical Research[b]		X	
Lumbar Puncture - CSF sample collection[g]		X	
Adverse Event Monitoring	X ---------- X		

[a] Screening procedures may be conducted over several visits during the Screening Period provided that the results are available to evaluate inclusion and exclusion criteria before allocation. The Screening Period my last up to approximately 4 weeks

[b] Informed consent for future biomedical research (FBR) samples must be obtained before the FBR sample for DNA analysis. The DNA sample for analysis should be obtained predose, on Day 1 as the last sample drawn, on allocated (treated) subjects only. The FBR sample can be obtained at a later date as soon as the informed consent is obtained, and with the next scheduled blood draw.

[c] Subjects should be resting in a semi-recumbent position for at least 5 minutes prior to having vital sign measurements obtained. Vital signs include heart rate, blood pressure, respiratory rate and temperature.

[d] To be administered at screening but results are not part of the inclusion/exclusion criteria.

[e] Diagnosis and narrative summary will be reviewed by external expert whose concurrence is required prior to allocation for AD subjects only.

[f] A urine sample will be collect for potential biomarker analysis. See Study Operations manual for details related to collection, storage and shipping.

[g] To be performed per local standard practice. Protocol-specific tubes will be used for collection. See the Study Operations Manual for collection, handling, storage and shipment details.

[h] MRI scans should be performed during the screening period after the subject has met all other screening inclusion and exclusion criteria. Previous scans performed within 1 year of signing consent 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 I/E criteria. The results of the MRI scan must be available before allocation to evaluate the inclusion/exclusion criteria.

[i] Safety follow up phone call should be made to assess for adverse experiences and concomitant medications; this assessment must include a full 14 days after the subject's last visit.

2. CORE PROTOCOL

2.1 OBJECTIVES AND HYPOTHESES

2.1.1 Primary

(1) To demonstrate operational integrity of MRL CSF sampling and assay procedures prior to their full deployment in the planned prodromal AD Phase II trial.

Hypothesis: The central laboratory is able to provide the investigators with accurate tau/$A\beta_{1-42}$ ratios within a reasonable timeframe, so that these data can be used to determine inclusion/exclusion criteria for future studies.

(2) To provide supportive evidence that the value of the tau/$A\beta_{1-42}$ ratio threshold for discriminating between AD patients and healthy elderly derived from the evaluation CSF samples in an ongoing study, is reasonable to use in the current and future studies.

Hypothesis: The true sensitivity is > 0.6 and the true specificity is > 0.4 for the tau/$A\beta_{1-42}$ ratio threshold value set in an ongoing study to be used for discriminating between AD patients and healthy elderly in the current study. The true sensitivity is expected to be 0.8 and the true specificity is expected to be 0.6.

2.2 SUBJECT/PATIENT INCLUSION CRITERIA

Healthy Elderly and Mild to Moderate Alzheimer's Disease Population

a. Each subject must be 60 to 80 years of age, inclusive, at the first visit.

b. Each subject must provide written informed consent for the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

c. Each subject must have a reliable and competent trial partner/caregiver who has a close relationship with the subject, has face to face contact at least three days a week for a minimum of six waking hours a week and is willing to accompany the subject to all visits. The trial partner/caregiver should understand the nature of the trial and adhere to trial requirements (e.g., visit schedules, evaluations).

d. Each subject must have results of a physical examination, vital signs, and ECG within normal limits or clinically acceptable to the investigator at screening.

e. Each subject must have results of clinical laboratory tests (complete blood count [CBC], blood chemistries, thyroid stimulating hormone [TSH], RPR and urinalysis) within normal limits or clinically acceptable to the investigator at screening.

f. Based on the investigator's judgment, each subject is able to speak, read, hear, and understand the language of the trial staff and the informed consent form, and possess

the ability to respond verbally to questions, follow instructions, and complete questionnaires. Each subject is also able and willing to adhere to visit schedules.

g. Each subject (or legal representative) must sign the informed consent form after the scope and nature of the investigation have been explained to them, and before screening assessments.

h. The subject has a Body Mass Index (BMI) ≤ 30 kg/m^2, at the pre-study visit (screening) visit. BMI is calculated by taking the subject's weight in kg and dividing by the subject's height in meters, squared.

i. Females of childbearing potential have a negative serum βhCG at screening. Female not of childbearing potential are defined by one of the following:

   1. has reached natural menopause (defined as ≥46 years of age with either

      a) ≥ 12 months of spontaneous amenorrhea or

      b) ≥ 6 months of spontaneous amenorrhea with serum follicle stimulating hormone (FSH) level > 40 IU/L as determined by the central laboratory. Pregnancy is to be ruled out by a negative serum βhCG prior to allocation

   2. has had a hysterectomy;

   3. has had a bilateral tubal ligation; or

   4. has had a bilateral oophorectomy (with our without a hysterectomy) and > 6 weeks have past since the surgery

Healthy Elderly Only

j. Each subject must have a Mini-Mental Status Examination (MMSE) score ≥ 28 at screening.

k. Obtain a score of 0 on the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SB)

l. Each subject must have a clear history of no cognitive and functional decline over at least one year that is either a) documented in medical records or b) documented by history from an informant who knows the subject well.

Mild to Moderate Alzheimer's Disease Only

m. Each subject must meet the criteria for a diagnosis of probable AD based on both a) the 1984 National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria (Appendix 6.3) and b) the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria for AD (Appendix 6.4).

n. Each subject must have an MMSE score ≥ 15 and ≤ 26 at screening.

o. Each subject must have a clear history of cognitive and functional decline over at least one year that is either a) documented in medical records or b) documented by history from an informant who knows the subject well.

p. Each subject must have an MRI scan at the screening visit to rule out non-AD conditions contributing to cognitive dysfunction. A scan that has been taken within the previous year may be used, but either the scan or the diagnostic report must be made available for the investigator to independently assess.

q. If a subject is receiving an acetylcholinesterase inhibitor and/or memantine, the dose must be stable for at least the last 3 months before screening, and the subject must be willing to remain on the same dose for the duration of the trial.

2.3 SUBJECT/PATIENT EXCLUSION CRITERIA

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

a. The subject has a Rosen modified Hachinski Ischemia Score > 4 at screening.

b. The subject has a known history of stroke that is clinically important in the investigator's opinion.

c. The subject has evidence of a clinically relevant neurological disorder other than the disease being studied (i.e., probable AD for AD cohort only) at screening, including but not limited to: vascular dementia, Parkinson's disease, frontotemporal dementia, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, progressive supranuclear palsy, dementia with Lewy bodies, other types of dementia, neuro-syphilis or head trauma with loss of consciousness that led to persistent cognitive deficits.

d. The subject has a history of seizures or epilepsy within the last 5 years before screening.

e. The subject has evidence of a clinically relevant or unstable psychiatric disorder, based on DSM-IV-TR criteria, including schizophrenia or other psychotic disorder, bipolar disorder, major depression, or delirium. Major depression in remission is not exclusionary.

f. The subject has a history of alcoholism or drug dependency/abuse within the last 5 years before screening.

g. The subject is unwilling or not eligible to undergo an MRI scan unless a prior MRI is available (see MRI Technical Manual for details).

h. The subject's MRI scan obtained at Screening shows evidence of a clinically significant neurological disorder other than probable AD or > 4 cerebral microhemorrhages (regardless of their anatomical location or diagnostic characterization as "possible" or "definite"), a single area of superficial siderosis, evidence of a prior macrohemorrhage, > 3 lacunar infarcts, or any cortical infarct over 5 mm.

i. The subject has a history of hepatitis or liver disease that, in the opinion of the investigator, has been active within the 6 months prior to screening.

j. The subject has a recent or ongoing, uncontrolled, clinically significant medical condition within 3 months of the screening visit (such as, but not limited to, diabetes, hypertension, thyroid or endocrine disease, congestive heart failure, angina, cardiac or gastrointestinal disease, dialysis, or abnormal renal function) other than the condition being studied such that, in the judgment of the investigator, participation in the trial would pose a significant medical risk to the subject. Controlled comorbid conditions (including diabetes, hypertension, heart disease, etc.) are not exclusionary if stable within three months of the screening visit. All concomitant medications, supplements, or other substances should be kept as stable as medically possible during the trial.

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

k. The subject has a history of malignancy occurring within the 5 years immediately before screening, except for a subject who has been adequately treated for

    1. basal cell or squamous cell skin cancer,

    2. in situ cervical cancer, or

    3. localized prostate carcinoma; or

    4. who has undergone potentially curative therapy with no evidence of recurrence for ≥ 3 year post therapy, and who is deemed at low risk for recurrence by her/his treating physician.

l. The subject has

    1. clinically significant vitamin B_{12} or folate deficiency in the six months immediately before screening, or

    2. vitamin B_{12} or folate deficiency in addition to increased serum homocysteine and methylmalonic acid levels at screening as determined by laboratory normal values.

m. The subject is pregnant, is attempting to become pregnant, or is nursing children.

n. The subject has any clinically significant condition or situation, other than the condition being studied, that, in the opinion of the investigator, would interfere with the trial evaluations or optimal participation in the trial.

o. The subject has used any investigational drugs or has been participating in any other clinical trial within the 30 days immediately before screening.

p. The subject has tested positive for HIV or has serologic evidence of an active Hepatitis B infection.

q. Subject has a history of clinically significant deep venous thrombosis (DVT), thrombophlebitis, or coagulopathy.

r. Subject has a history or signs/symptoms of lumbar spine/disc disease including but not limited to scoliosis, herniation, or any other contraindication to lumbar puncture.

s. Subject has a history of a recent infection (e.g. meningitis, encephalitis) (within past month), significant immunodeficiency and/or hospitalization (within past year) for any reason.

t. Subject has recent history (within the past year) of migraine headaches.

u. Subject has a family or personal history of hemophilia.

v. Subject has a hypersensitivity to lidocaine.

w. Subject has a history of prior back surgery, use of anticoagulants, low platelets, prolonged PT or PTT (based on screening labs), ongoing infection of overlying skin area or an inability to lie on side for 30 min.

2.4 STUDY DESIGN AND DURATION

2.4.1 Summary of Study Design

This study is a multicenter worldwide trial to assess the tau/$A\beta_{1-42}$ ratio in CSF from healthy elderly and mild to moderate AD patients. Subjects will undergo several assessments to determine either cognitive health (HE population) or probable mild to moderate AD (m/m AD population) based on the 1984 NINCDS-ARDRA Criteria and DSM-IV-TR. ADAS-Cog and ADCS-ADL will be performed for future comparison to other diagnostic measures of AD. All screened subject will also have urine collected for biomarker analysis.

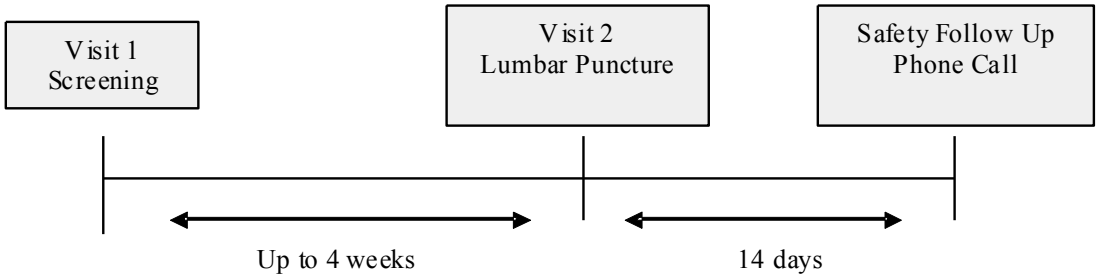
Eligible subjects will return to the clinic for the treatment visit within approximately 4 weeks to have a lumbar puncture for CSF collection. The lumbar puncture should be performed per local standard procedures; however, protocol-specific collection tubes supplied by the sponsor will be used for collection, handling and storage of the samples. See the study operations manual for details related to CSF collection. Approximately 7 mL of CSF will be obtained with no subject having more than 8 mL taken for any reason.

Urine samples for biomarker analysis will also be collected during this visit. Subjects will remain at the clinic for at least 4 hours after the procedure or until the investigator feels it is safe for them to be released.

Subjects will be contacted by phone to assess for adverse events and concomitant medications; this assessment must encompass a full 14 days post the last treatment visit. The assessment must cover 14 days post the treatment visit. See **Error! Reference source not found.** for study design schematic.

Figure 2-1

Study Design Schematic



The duration of the study will be approximately 12 months. The duration for each subject/patient to complete the study will be approximately 4-6 weeks from screening to poststudy.

2.4.2 Treatment Plan

There is no study drug administered in this trial. Eligible subjects will be allocated to the trial upon successful completion of all inclusion/exclusion criteria outlined in Section 2.2 and 2.3.

2.5 LIST OF PHARMACODYNAMIC MEASUREMENTS

CSF will be assayed for tau and $A\beta_{1-42}$ to determine the ratio. ADAS-Cog and ADCS-ADL will be collected for future comparison to other diagnostic criteria.

2.6 LIST OF SAFETY MEASUREMENTS

Safety will be monitored throughout the study by physical exam, laboratory safety tests, vital sign measurements and 12 lead ECGs. These procedures may also be performed at unscheduled time points if deemed clinically necessary by the investigator.

Adverse events will be assessed at each visit. Subjects will be monitored for adverse experiences throughout the study.

Adverse Events and Serious Adverse Events will be captured as per Section 3.4.

2.7 STATISTICAL ANALYSIS PLAN SUMMARY

2.7.1 Responsibility for Statistical Analyses

The statistical analyses of the data obtained from this study will be the responsibility of the Experimental Medicine Statistics (EM STATS) Department of Merck Research Laboratories (MRL) who will work in close collaboration with Merck's Experimental Medicine Department. 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 an Experimental Medicine Results Memo (EMRM) for the study, as appropriate.

2.7.2 Endpoints

Primary Endpoint

Fifty-five clinically diagnosed mild to moderate Alzheimer's Disease patients (AD) and 55 healthy elderly (HE) control subjects will each be classified as either having AD, or not, according to a CSF tau/$A\beta_{1\text{-}42}$ ratio threshold. The specific CSF tau/$A\beta_{1\text{-}42}$ ratio threshold to be used in the current study will be determined from an ongoing sampling study which is measuring CSF tau/$A\beta_{1\text{-}42}$ ratios for HE and AD patients, using the MRL Tween-based assay.

2.7.3 Statistical Methods

2.7.3.1 Primary Hypotheses

Primary Hypothesis #1

The EM Department of MRL will assess the quality and timeliness of CSF sample collection and the subsequent Tween assay of CSF tau/$A\beta_{1\text{-}42}$ ratios, as performed by the central lab.

Primary Hypothesis #2

AD patients and HE controls will be classified as either having AD, or not, according to the CSF tau/$A\beta_{1\text{-}42}$ ratio threshold from the ongoing sampling study, and the results will be displayed in a table similar to the one below where TP = true positive count, FN = false negative count, FP = false positive count, and TN = true negative count.

Tau/$A\beta_{1-42}$ Ratio

		AD	Healthy	
Clinical Diagnosis	AD	**TP**	**FN**	55
	Healthy	**FP**	**TN**	55
		TP+FP	FN+TN	110

The primary emphasis of the statistical analysis is to estimate the sensitivity (true positive rate, TPR) and specificity (true negative rate, TNR) of the CSF tau/$A\beta_{1-42}$ ratio threshold value as a potential AD biomarker. Sensitivity will be estimated by the proportion of AD patients for which the CSF tau/$A\beta_{1-42}$ ratio threshold yields an AD classification, TPR = TP / (TP+FN). Specificity will be estimated by the proportion of HE controls for which the CSF tau/$A\beta_{1-42}$ ratio threshold yields a healthy classification, TNR = TN / (TN+FN). For both sensitivity and specificity, lower one-sided 95% confidence intervals (CIs) for the true values will be constructed [1].

2.7.3.2 Exploratory Analyses

Which exploratory analyses are performed is dependent upon what information is of interest at the time this study is run. Some potential questions include but are not limited to: What statistical analyses were used in the ongoing sampling study? Is there an interest in duplicating the statistical analyses performed in the ongoing sampling study? What information is provided to us from the ongoing sampling study? Is there an interest in comparing the results of the two studies? Is there an interest in combining the information from the two studies, or updating the information from the ongoing sampling study to the current study?

The exploratory analyses focus on receiver operating characteristic (ROC) curves, and Bayesian updates to sensitivity, specificity, threshold values, and ROC curves. See the DETAILS section of the protocol for more information.

2.7.3.3 Unplanned Interim Analysis of the Data – Primary Hypothesis # 2

Given the timing of the current study, the ongoing development of a definitive assay, and the timing of subsequent studies using the CSF assay, the recruitment of either or both ADs (n=55) and HE subjects (n=55) may be incomplete (e.g., n=20, 30, or 40) when the prodromal study starts. The data accumulated in the current study may need to be assessed prior to starting subsequent studies.

Sequential Repeated Confidence Intervals

Once the incomplete sample sizes are known, a sequential repeated confidence interval (RCI) strategy will be built planning to estimate both sensitivity and specificity, and the corresponding confidence intervals, at the interim point, and then again at the completion of the study [2].

Bayesian Updates

In addition to the repeated confidence intervals, a Bayesian update of the sensitivity and specificity, and corresponding credible intervals, may be computed. Also of interest are the predictive distributions corresponding to the sensitivity and specificity for the remaining ADs and HEs to be recruited to complete the current study, or projecting beyond that to the prodromal study.

Primary Hypothesis # 1

The unplanned interim sequential RCIs and Bayesian updates were described in terms of Primary Hypothesis # 2. The same approaches can be taken with Primary Hypothesis # 1, provided that the CSF sample collection and the subsequent assay of CSF tau/$A\beta_{1-42}$ ratios as performed by the central lab, can be classified as either a "success" or "failure" for each AD or HE based upon some quality and timeliness criteria.

2.7.3.4 Pharmacogenetics (PGt) studies

Exploratory pharmacogenetics (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Pharmacogenetic studies will be conducted with Biostatistics design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials.

2.7.4 Multiplicity

Primary Hypothesis #2

Planned Analyses: Since the two 95% CIs are independent, together they form a rectangular joint > 90% (0.95*0.95 =.9025) confidence region for specificity and sensitivity [3].

Unplanned Interim Analyses: Sequential repeated confidence intervals [2] will be used for both sensitivity and specificity estimation which further accommodates achieving an overall confidence level of 90%.

2.7.5 Sample Size Precision, and Power

Primary Hypothesis #2

Planned Analyses

To calculate power for this study, it was assumed for the CSF tau/$A\beta_{1-42}$ ratio threshold determined from the ongoing sampling study, that the true sensitivity = 0.8 and the true specificity = 0.6. Simulations performed previously by Biometrics Research indicate that 51 AD patients are sufficient to show with 0.93 power (α=.05, one-tailed) that the true sensitivity is greater than 0.6. Similarly, with 51 control subjects there is 0.88 power (α=.05, one-tailed) to show that the true specificity is greater than 0.4. Therefore, the lower bounds on the one-sided CIs observed for sensitivity and specificity should not, with their assigned probabilities, be more than 0.20 below their true value.

The null hypothesis that the sensitivity is ≤ 0.60 or that the specificity is ≤ 0.40, will be rejected in favor of the alternative that the sensitivity > 0.60 and the specificity is > 0.40, if the hypothesized point (sensitivity=0.60, specificity=0.40) does not lie in the joint >90% confidence region. The power for rejecting the null hypothesis is >0.8 (0.93 x 0.88 = 0.8184).

Unplanned Interim Analyses

The sample sizes for ADs and HEs will not be known until the interim analyses become necessary. Assuming that the true sensitivity =.80 and that either 20, 30, or 40 ADs have completed at the time the unplanned analysis becomes necessary, then there is approximately 0.9 power (α=.05, one-tailed) to demonstrate that the true sensitivity is greater than 0.49, 0.53, and 0.58, respectively. The corresponding values for an assumed specificity in HEs of 0.6 are 0.25, 0.33, and 0.36. The overall power (sensitivity and specificity combined) is approximately 0.81.

Product: Non-Product 1
Protocol/Amendment No.: 261-00

3. PROTOCOL DETAILS

3.1 RATIONALE

3.1.1 Rationale for This Study

Background. Alzheimer's disease (AD) is the leading cause of dementia, and there is no effective disease-modifying therapy at present. AD is characterized by specific histopathological features including amyloid deposits (plaques), neurofibrillary tangles, and neuronal degeneration. The "amyloid hypothesis" posits that amyloid-β (Aβ) peptides aggregate into complexes, such as fibrils and plaques, which subsequently trigger the development of tau-related neurofibrillary tangles. These tangles are thought to be the more proximal cause of neuronal degeneration. Aβ pathology appears to begin years before the onset of AD and is thought at some point to trigger tau pathology, neural degeneration, and the subsequent gradual emergence of clinical symptoms. As amyloid plaques continue to accumulate, tangle pathology spreads to a variety of brain regions, leading to progressive neuronal degeneration, brain atrophy, and cognitive decline.

Aβ peptides are produced through cleavage of amyloid precursor protein (APP) by three distinct proteases: α-secretase, BACE1 (β site APP cleaving enzyme 1; also known as β-secretase), and γ-secretase. Most APP is processed by α- and γ-secretases to generate nonamyloidogenic peptides. However, 5-10% of APP is cleaved by BACE1 and γ-secretase to generate pathogenic Aβ peptides ($A\beta_{1-40}$ and $A\beta_{1-42}$). Deletion of BACE1 in mice eliminates Aβ in both the plasma and the brain. Thus, inhibition of BACE1 is a potential therapeutic strategy for slowing or halting progression of AD.

Clinical trials for AD have been hampered by slow clinical progression, clinical misdiagnosis, and lack of predictive biomarkers. Recent studies suggest that analysis of cerebrospinal fluid (CSF), specifically, levels of the proteins tau and $A\beta_{1-42}$, can improve subject selection for clinical studies. The CSF tau/$A\beta_{1-42}$ ratio, in conjunction with clinical exam data, can improve the likelihood that a given trial subject actually has AD, as opposed to another dementing disorder. Thus, use of CSF biomarkers can improve the sensitivity and power of clinical trials in AD. As such, CSF biomarkers are envisioned to be part of the selection criteria for upcoming and ongoing Phase 2 trials of disease modifying compounds. It will be important to determine if CSF tau/$A\beta_{1-42}$ ratio can operationally be used to facilitate subject selection, especially in a multicenter, multinational AD disease modification trial.

The goals of the current study are: 1) to determine the feasibility of CSF sample collection to aid in patient selection, and 2) to confirm the specificity and sensitivity of the CSF assay in distinguishing healthy elderly subjects from AD patients.

Biomarkers Aid Patient Selection for AD Trials. The ability to detect slowing of disease progression in a clinical trial of AD will depend on proper selection of patients. While the diagnosis of advanced AD is not difficult, patients with advanced stage AD are not likely to benefit from disease-modifying therapy, as the degree of neuronal destruction has

progressed too far. Therefore, the patients who are most likely to benefit from a disease-modifying therapy will be those who are relatively early in the disease process. For AD, this category is called prodromal AD, which is a subset of the condition known as mild cognitive impairment (MCI). MCI represents a transitional state between normal cognitive change associated with aging and Alzheimer's disease. However, only a subset of patients carrying the MCI diagnosis will go on to develop full-blown AD (MCI-AD), with other MCI patients having non-AD conditions (stable MCI). Biomarkers such as cerebrospinal fluid (CSF) proteins or PET imaging for amyloid deposition can help predict those subjects with MCI who in fact have prodromal AD. Throughout the literature, CSF measurements of tau and $A\beta_{1-42}$ have demonstrated the ability to predict which subjects with MCI will go on to have AD. For example, in one study total tau and $A\beta_{1-42}$ at baseline yielded a sensitivity of 95% and a specificity of 83% for detection of incipient AD in MCI patients [4]. Thus, including biomarker inclusion criteria helps to insure that study subjects do in fact have prodromal AD, and will decrease the required sample size.

CSF Assays for tau and $A\beta_{1-42}$. Multicenter collaborative studies such as ADNI (Alzheimer's Disease Neuroimaging Initiative) have demonstrated that the CSF tau/$A\beta_{1-42}$ ratio is clinically useful. $A\beta_{1-42}$ is a cleavage product of the amyloid precursor protein (APP), generated by the enzymatic activities of β-secretase and γ-secretase, and thought to be a biomarker relevant to the AD pathological process. $A\beta_{1-42}$ levels in the CSF tend to decline during the disease course of AD. Tau is a neuronal protein, and its increase in CSF levels is thought to reflect neuronal injury. The ratio of tau/$A\beta_{1-42}$ has been incorporated into the diagnostic criteria of not only AD [5], but also of the prodromal state of mild cognitive impairment (MCI) [6]. MRL has found that $A\beta_{1-42}$ protein can adhere to plastic, potentially biasing any assay of $A\beta_{1-42}$. Addition of the detergent Tween to CSF collection tubes can correct the issue of $A\beta_{1-42}$ adhesion, yet existing datasets reflect samples that were not collected with Tween. Thus, the cutoff criteria to discriminate between AD subject and healthy elderly need to be determined with Tween present in collection tubes. In an ongoing study, CSF tau/$A\beta_{1-42}$ ratios are being determined for cohorts of HE and AD patients, using the MRL Tween-based assays. The cutoff for distinguishing HE and AD emanating from this ongoing study will be applied in to the current study.

Feasibility of CSF Collection. The ideal patient population for testing disease modification is MCI patients that in fact have prodromal AD (MCI-AD). Biomarkers such as CSF tau/$A\beta_{1-42}$ ratio and amyloid PET imaging help identify those MCI subjects whose pathology is due to AD [6]. Any disease modification clinical trial in AD is likely to require over 100 clinical sites, with multiple patients being enrolled at each site. An important milestone to demonstrate is the feasibility of collecting CSF samples from sites worldwide, as well as the feasibility of shipping and analyzing these samples in a timely enough fashion to support patient recruitment. As current conceptions of disease modification trials envision world-wide participation, it is an important objective of the current study to demonstrate the operational feasibility of collecting CSF samples and obtaining tau/$A\beta_{1-42}$ ratio results in a reasonable timeframe, approximately 1-2 weeks, to inform inclusion/exclusion criteria in future studies reliably from sites around the world.

This study will test operational feasibility using sites in the United States, Europe, South America, Australia and Asia. It is anticipated that logistical problems arising in the current study will inform the design and execution of subsequent AD disease modification trials.

Objectives for the Current Study. In order for CSF tau/$A\beta_{1-42}$ ratio to be useful for patient selection, several criteria must be fulfilled:

- Sites from different countries must succeed logistically in being able to collect and ship CSF samples and relevant clinical information.
- The central vendor managing the CSF assay must be able to turn around data in a reasonable time frame, approximately 1-2 weeks.
- The current CSF assay must be able to discriminate between mild to moderate AD patients and healthy elderly subjects. Using the cutoff ratio generated from an separate ongoing study, the sensitivity and specificity of the CSF diagnostic test will be determined on samples from AD patients and healthy elderly in the current study

Using Cutoff Values from AD Patients to Aid in Selection of MCI patients. Use of CSF biomarkers in AD clinical trials is a nascent enterprise and several issues bear consideration. Assay variability is well-documented, especially between sites. Addition of Tween to the CSF collection tubes promises to improve the variability of the $A\beta_{1-42}$ assay, but other published assays have not used Tween. Hence, there are no cutoff (HE vs. AD) values in the literature that are applicable to the current study. Importantly, a recent opinion from the European Medicines Agency has endorsed the use of CSF biomarkers stating "the CSF biomarker signature based on a low $A\beta_{1-42}$ and a high tau qualifies to identify MCI patients as close as possible to the prodromal stage of AD" [18]. However, there is no agreed upon cutoff value for tau/$A\beta_{1-42}$ ratio that serves as a community standard. For this reason, an ongoing Merck study is measuring tau/$A\beta_{1-42}$ ratios in several cohorts of HE and AD. The cutoff--the tau/$A\beta_{1-42}$ ratio that optimally distinguishes HE from AD based on clinical diagnosis—will be the value applied in the current study.

As disease modification trials will target MCI-AD patients, the ideal patient population in which to determine tau/$A\beta_{1-42}$ ratio cutoff would be MCI-AD patients. However, several points justify using HE and AD to establish and confirm these cutoffs. First, the tau/$A\beta_{1-42}$ ratio imperfectly distinguishes HE from AD; that is, there is some overlap between these populations in this CSF measure. Next, in several published papers, the cutoff that distinguishes MCI-AD from stable MCI is the same cutoff that distinguishes HE from AD. Although there is some overlap, measuring tau and $A\beta_{1-42}$ can yield important information, yielding a sensitivity of 95% and a specificity of 85% for detection of incipient AD in MCI patients [4]. Although the likelihood is that using a Tween-based assay will generate a different ratio cutoff from non-Tween assays, said cutoff (which distinguished HE vs AD) is likely to discriminate stable MCI from MCI-AD. The definitive method for validating the cutoff for the Tween-based assay is to identify a cohort of MCI subjects and to follow them prospectively. However, this approach would

take several years, and replicates many other independent efforts that have returned the same essential result. Finally, as future POC trials envision using not only CSF measures but also amyloid PET imaging, the tau/$A\beta_{1-42}$ ratio will not stand in isolation. Using amyloid PET imaging in parallel to CSF measures would provide bridging information to published reports.

3.1.2 Rationale for Assay Method

CSF Diagnostic Assays are Variable. Several commercial kits are available to measure tau and $A\beta_{1-42}$. Importantly, available assays often demonstrate large differences in absolute values. For example, although there was an approximately 2- to 6-fold difference between two commercially available assays, both assays yielded similar correlations to amyloid load (as assessed by PET scanning with the amyloid imaging agent Pittsburgh compound B [7]. Such results highlight the need to develop assay-specific cutoff values. Concern about assay variability is a concern within the AD community such that an external quality control program has been developed by the Alzheimer's Association [8]. Importantly, most commercial assays do not include the detergent Tween,, again highlighting to the importance of developing internal MRL assay parameters. Measurements of CSF AD biomarkers show large between-laboratory variability, likely related to difference in analytical procedures and reagents used (reviewed in [8]). While within-center coefficients of variation (CV) are generally low, 10-15%, interlaboratory CVs are significantly higher, approximately 25 to 35%. Ideally, samples to be compared would be analyzed within a single laboratory.

CSF Assay. One potential source of assay variability may be the propensity of $A\beta_{1-42}$ to adhere to plastic, as detailed in a recent publication from the Clinical Developmental Laboratory of MRL [9]. $A\beta_{1-42}$ is a hydrophobic peptide that binds to polypropylene; depending on the manufacturer, incubation of CSF in polypropylene tubes resulted in reductions of $A\beta_{1-42}$ of up to 62.7%. The adherence of $A\beta_{1-42}$ to plastic can be counteracted by addition of the detergent Tween to the collection tubes. Thus, adding Tween-20 (at a final concentration of 0.05%) has the potential to greatly increase the signal to noise ratio of the CSF $A\beta_{1-42}$ assay. Given this uncertainty, it is imperative to measure CSF samples from healthy elderly and AD patients in order to define sensitivity and specificity of the CSF tau/$A\beta_{1-42}$ ratio. CSF diagnostic assay is envisaged to be used as an inclusion criterion in the planned prodromal POC trial. These measures of sensitivity and specificity will be obtained on a population that should serve as a "positive control"; in other words, at a minimum, the assay should be able to discriminate between AD and healthy elderly with high sensitivity and specificity. While the addition of 0.05% of Tween should improve signal to noise, if the current assay does not demonstrate adequate sensitivity and specificity in discriminating between AD and healthy elderly, that result would comprise a "No-Go" for the use of CSF biomarkers as part of the inclusion criteria for the prodromal AD trial.

3.1.3 Rationale for Future Biomedical Research

Merck will conduct Future Biomedical Research on DNA (blood) specimens collected during this clinical trial.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs, and/or to ensure that subjects receive the correct dose of the correct drug at the correct time. The details of this Future Biomedical Research sub-trial are presented in Appendix 6.5 Collection and Management of Specimens for Future Biomedical Research.

3.2 STUDY PROCEDURES

3.2.1 Concomitant Medication

In general, the use of concomitant medication is permitted within this study; however, use must relate to the documented medical history, prophylaxis, or an adverse event of the subject. Any concomitant medication must be assessed by the investigator and discussed with the sponsor as appropriate.

Subjects must not take any medication that can increase bleeding risk such as anticoagulants. Aspirin is not contraindicated for this protocol.

3.2.2 Procedures

3.2.2.1 Timing of Procedures

Study procedures should be completed as close to the scheduled time as possible. Any nonscheduled procedure required for urgent evaluation of safety concerns takes precedence over all routine scheduled procedures.

3.2.2.2 Details for the Conduct of Procedures

Weight and Height

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

Body Temperature

Body temperature will be measured with an oral or tympanic thermometer. The same method (e.g., oral or tympanic) must be used for all measurements for each individual subject and should be the same for all subjects.

Laboratory Safety Tests (Appendix 6.1 and 6.2)

Laboratory safety tests will be performed after at least approximately 4-hour fast.

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

Subjects should be resting in a semi-recumbent position for at least 5 minutes prior to having vital sign measurements obtained. Semi-recumbent vital signs will include heart rate (HR) and blood pressure (BP) and respiratory rate (RR) at time points indicated in the flow chart. The correct size of the blood pressure cuff and the correct positioning on the subjects' arm is essential to increase the accuracy of blood pressure measurements. The same method (e.g., manual or automated) must be used for all measurements for each individual subject and should be the same for all subjects.

12-Lead ECG

Special care must be taken for proper lead placement. Subjects may need to be shaved to ensure proper lead placement. Female subjects may need to remove their bra.

Subjects should be resting in a semi-recumbent position for at least 5 minutes prior to having ECG readings obtained. If repeat ECGs are required the clinical site will decide if to either leave the electrodes in place or mark the position of the electrodes for subsequent ECGs.

Lumbar puncture

Lumbar puncture should be performed per local standard procedures with the exception of the collection tube. The central vendor will provide all required collection tubes for this procedure.

3.2.2.3 Screening Visit

Within approximately 4 weeks prior to the treatment visit, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Sections 2.2 and 2.3.

All subjects will be given a card identifying them as participants in a research study. The card will contain contact information (including direct telephone numbers) to be utilized in the event of an emergency.

Quality control is an essential part of all clinical trials. For AD trials, it is particularly important to monitor a) whether subjects selected for allocation meet entry criteria and b) clinical ratings. This trial will include a review by outside expert(s) of each m/m AD subject prior to allocation. This review may include all available medically relevant data, a narrative summary of the patient's history, and a review of videotapes/audiotapes (or recorded webcams) of key clinical interviews performed that may or may not be obtained at the screening visit.

Rater performance on clinical assessments will be carefully evaluated and monitored to ensure and maintain adequate reliability. Details can be found in the Study Operations Manual. In order to qualify for the trial, raters must be approved by the sponsor. To ensure the continued quality of the assessments (MMSE, CDR, ADAS-Cog, and ADCS-ADL), raters may be asked to webcam (or videotape/audiotape) interviews and ratings at some or all visits. Some or all of these recorded interviews, if obtained, may be reviewed by outside experts. Raters will be provided feedback on the quality of their interviews and ratings by the outside experts by e-mail, telephone or in meetings. Routine rater meetings may be conducted to assess and maintain reliability for the duration of the trial. Raters who do not perform adequately may be required to undergo additional remediation or may be replaced.

3.2.2.4 Treatment Visit

Eligible subjects that have been confirmed by the external rater as acceptable will return to the clinic for CSF collection. Subjects must comply with study restrictions to have the procedure performed.

The first 2 mL of CSF will be discarded in a non-protocol specific collection tube to clear out any blood that may contaminate the sample. The next approximately 4 mL will be collected in multiple tubes that are specific to the protocol and provided by a central vendor. An approximate total of 6 mL of CSF is targeted for collection with no more than 8 mL collected for any reason. CSF samples will be shipped on a regular basis as detailed in the Study Operations Manual. The central laboratory must provide the study investigator or the sponsor with the tau and $A\beta_{1-42}$ values within approximately one week of receipt of the sample. Refer to the Study Operations Manual for details related to CSF collection, handling, storage and shipping information.

Vital signs will be taken pre and post collection to monitor the safety of the subject. They will remain at the site for a minimum of 4 hours post completion of the CSF collection or until the investigator feels it is safe for them to leave.

3.2.2.5 Poststudy Follow Up

Subjects will be called by the site staff to assess for adverse experiences and concomitant medication used to treat adverse experiences. Assessment of AEs/concomitant medications must cover a full 14 days post the last treatment procedure.

If a subject discontinues at any time during the course of the study, the subject will be contacted for a poststudy visit to assess for adverse experiences and concomitant medication used to treat adverse experiences during the 14 day period following the last protocol specified procedure.

3.2.2.6 Informed Consent

3.2.2.6.1 General Informed Consent

The investigator must obtain documented consent from each potential subject in future biomedical research or when an investigational drug is administered to the subject in a clinical study, prior to any study related procedures being performed.

Consent must be documented by the subject's dated signature on a Consent Form along with the dated signature of the person conducting the consent discussion. A copy of the signed and dated consent form should be given to the subject before participating in the trials.

3.2.2.6.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

3.2.2.6.3 Future Biomedical Research

The following specimen is to be obtained as part of Future Biomedical Research:

- Blood for genomics use

3.2.2.7 Assignment of Baseline Number

A baseline or screening number is assigned to the subject upon signing the consent form to identify the subject for all procedures that occur prior to allocation. Each baseline or screening number will be assigned to only one subject.

3.2.2.8 Allocation

Each subject will be assigned an allocation number at the treatment visit prior to CSF collection procedure. The allocation number will be used to identify the subject for all procedures occurring after assignment.

A single patient/subject cannot be assigned more than 1 allocation number.

In a situation where rerandomization of the subjects/patients is planned (e.g., study extension periods), the rerandomization is done based on a new allocation schedule, however each subject/patient retains his/her original allocation number. Only the treatment regimen associated with the rerandomization period or phase may change.

3.2.2.9 Discontinuation/Withdrawal from Study

Subjects/patients may withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a subject/patient may be withdrawn by the investigator or the SPONSOR if he/she violates the study plan or for administrative and/or other safety reasons. The investigator or study coordinator must notify the SPONSOR immediately when a subject/patient has been discontinued/ withdrawn due to an adverse experience (telephone or FAX). When a subject/patient discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse experiences which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 3.4 SAFETY MEASUREMENTS - DETAILS.

Subjects/patients who discontinue from the study for reasons unrelated to the study (e.g., personal reasons) will be replaced as required for the study to meet its objectives. The decision to remove a subject/patient and to replace dropouts will be made jointly by the investigator, SPONSOR Clinical Monitor, and SPONSOR study statistician. The replacement will generally receive the same treatment or treatment sequence (as appropriate) as the allocation number replaced. Both the replacement and originally allocated number will be unique numbers.

3.2.2.10 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by writing to the principal investigator for the main trial. If medical records for the main trial are still available, the Investigator will contact the Sponsor using the designated mailbox PPD and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the Investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory agencies to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

3.2.2.10.1 Study Completion and Termination

Definition of Study Completion

Study completion is defined as the date the last subject completes the final visit in the study.

Given the unpredictable nature of early phase I studies, it may exceptionally be necessary to keep the study open for gathering/reviewing additional supportive data (preclinical and/or clinical) to optimally complete the objective(s) of the study. In this case the competent authority(ies) and the ethics committee(s) will be appraised of the maximum extension of the duration of the study beyond the last subject out and the justification for keeping the study open. If necessary, the appropriate amendments to the protocol will be generated.

Definition of Study Termination

Study termination is defined as a permanent discontinuation of the study due to unanticipated concerns of safety to the study subjects or availability of other new data (pharmacokinetic, pharmacodynamic, efficacy, biologic etc.) arising from clinical or preclinical studies. A study may be paused during review of newly available preclinical/clinical safety, pharmacokinetic, pharmacodynamic, efficacy, or biologic data, or other issues of interest or potential concern prior to a final decision for continuation or termination of the study.

3.3 PHARMACODYNMAIC MEASUREMENTS

3.3.1 Clinical and Laboratory Measurements for Pharmacodynamics

- tau/Aβ_{1-42} ratio as measured in CSF

3.3.2 Adjudication Procedures

Confirmation of mild to moderate AD will be obtained by a third party adjudicator.

3.4 SAFETY MEASUREMENTS

3.4.1 Clinical and Laboratory Measurements for Safety

Physical examination, neurological examination, laboratory safety tests, vital signs and ECGs will be performed at various times throughout the study. Subjects will be assessed for adverse events during the study. Any safety procedures may be done at unscheduled time points, if deemed necessary by the investigator or sponsor

3.4.2 Recording Adverse Experiences

An adverse experience is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the SPONSOR's product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of

a preexisting condition which is temporally associated with the use of the SPONSOR's product, is also an adverse experience.

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

Adverse experiences may occur in the course of the use of a Merck product in clinical studies or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse, and from withdrawal.

Adverse experiences may also occur in screened subjects/patients during any preallocation baseline period as a result of a protocol-specified intervention including washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

Such events will be recorded at each examination on the Adverse Experience Case Report Forms/Worksheets.

3.4.3 Definition of an Overdose for This Protocol

3.4.3.1 Reporting of Overdose to SPONSOR

If an adverse experience(s) is associated with ("results from") the overdose of test drug or vaccine, the adverse experience(s) is reported as a serious adverse experience, even if no other criteria for serious are met.

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

All reports of overdose with and without an adverse experience must be reported within 24 hours to one of the individuals listed on the sponsor contact information page found in the Administrative Binder.

3.4.4 Reporting of Pregnancy to SPONSOR

Although not considered an adverse experience, it is the responsibility of investigators or their designees to report any pregnancy in a subject/patient (spontaneously reported to them) which occurs during the study or within 14 days of completing the study. All subjects/patients who become pregnant must be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported to one of the individuals listed on the SPONSOR Contact Information page found in the Administrative Binder.

3.4.5 Immediate Reporting of Adverse Experiences to the SPONSOR

3.4.5.1 Serious Adverse Experiences

Any serious adverse experience, including death due to any cause, which occurs to any subject/patient entered into this study or within 14 days following cessation of treatment or within the established off therapy follow-up period for safety described in the protocol, whether or not related to the investigational product, must be reported within 24 hours to one of the individual(s) listed on the contact information page.

Additionally, any serious adverse experience considered by an investigator who is a qualified physician to be possibly, probably, or definitely related to the investigational product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to one of the individuals listed on the sponsor contact information page found in the administrative binder.

All subjects/patients with serious adverse experiences must be followed up for outcome.

3.4.5.2 Selected Nonserious Adverse Experiences (if applicable)

These selected non-serious adverse experiences are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Experience Case Report Forms/Worksheets.

3.4.6 Evaluating Adverse Experiences

Refer to Table 3-1 for instructions in evaluating adverse experiences.

Table 3-1

An investigator who is a qualified physician, will evaluate all adverse experiences as to:

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

Relationship to test drug (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the dose of test drug discontinued or 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 test drug; or (3) the study is a single-dose drug study.)
	Rechallenge	Was the subject/patient reexposed to the test drug 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.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE TEST DRUG, OR IF REEXPOSURE TO THE TEST DRUG POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT/PATIENT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.
	Consistency with Study Drug Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the test drug or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a drug relationship).**
Yes, there is a reasonable possibility of drug relationship.		There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to the administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. **Depending on data collection method employed, drug relationship may be further graded as follows:**
	Definitely related	There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge is positive. Rechallenge (if feasible) is positive. The AE shows a pattern consistent with previous knowledge of the test drug or test drug class.
	Probably related	There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge (if performed) is positive.
	Possibly related	There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE could have been due to another equally likely cause. Dechallenge (if performed) is positive.
No, there is not a reasonable possibility of drug relationship		Subject did not receive the test drug OR temporal sequence of the AE onset relative to administration of the test drug is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.) **Depending on data collection method employed, drug relationship may be further graded as follows:**
	Probably not related	There is evidence of exposure to the test drug. There is another more likely cause of the AE. Dechallenge (if performed) is negative or ambiguous. Rechallenge (if performed) is negative or ambiguous.
	Definitely not related	The subject/patient did not receive the test drug. OR Temporal sequence of the AE onset relative to administration of the test drug is not reasonable. OR There is another obvious cause of the AE.

3.4.7 SPONSOR Responsibility for Reporting Adverse Experiences

All adverse experiences will be reported to regulatory agencies, IRB/IECs, and investigators in accordance with all applicable global laws and regulations.

3.5 STATISTICAL ANALYSIS PLAN (SAP)

3.5.1 Responsibility for Statistical Analyses

The statistical analyses of the data obtained from this study will be the responsibility of the Experimental Medicine Statistics (EM STATS) Department of Merck Research Laboratories (MRL) who will work in close collaboration with Merck's Experimental Medicine Department. 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 an Experimental Medicine Results Memo (EMRM) for the study, as appropriate.

3.5.2 Endpoints

Primary Endpoint

Fifty-five clinically diagnosed mild to moderate Alzheimer's Disease patients (AD) and 55 healthy elderly (HE) control subjects will each be classified as either having AD, or not, according to a CSF tau/$A\beta_{1\text{-}42}$ ratio threshold. The specific CSF tau/$A\beta_{1\text{-}42}$ ratio threshold to be used in the current study will be determined from an ongoing sampling study which is measuring CSF tau/$A\beta_{1\text{-}42}$ ratios for HE and AD patients, using the MRL Tween-based assay.

3.5.3 Statistical Methods

3.5.3.1 Primary Hypotheses

Primary Hypothesis #1

The EM Department of MRL will assess the quality and timeliness of CSF sample collection and the subsequent Tween assay of CSF tau/$A\beta_{1\text{-}42}$ ratios, as performed by the central lab.

Primary Hypothesis #2

AD patients and HE controls will be classified as either having AD, or not, according to the CSF tau/$A\beta_{1\text{-}42}$ ratio threshold from the ongoing sampling study, and the results will be displayed in a table similar to the one below where TP = true positive count, FN = false negative count, FP = false positive count, and TN = true negative count.

Tau / $A\beta_{1-42}$ Ratio

		AD	Healthy	
Clinical Diagnosis	AD	**TP**	**FN**	55
	Healthy	**FP**	**TN**	55
		TP+FP	FN+TN	110

The primary emphasis of the statistical analysis is to estimate the sensitivity (true positive rate, TPR) and specificity (true negative rate, TNR) of the CSF tau/$A\beta_{1-42}$ ratio threshold value as a potential AD biomarker. Sensitivity will be estimated by the proportion of ADs for which the CSF tau/$A\beta_{1-42}$ ratio threshold yields an AD classification, TPR = TP / (TP+FN). Specificity will be estimated by the proportion of HE controls for which the CSF tau/$A\beta_{1-42}$ ratio threshold yields a healthy classification, TNR = TN / (TN+FN). For both sensitivity and specificity, lower one-sided 95% confidence intervals (CIs) for the true values will be constructed [1].

3.5.3.2 Exploratory Analyses

Which exploratory analyses are performed is dependent upon what information is of interest at the time this study is run. Some potential questions include but are not limited to: What statistical analyses were used in the ongoing sampling study? Is there an interest in duplicating the statistical analyses performed in the ongoing sampling study? What information is provided to us from the ongoing sampling study? Is there an interest in comparing the results of the two studies? Is there an interest in combining the information from the two studies, or updating the information from the ongoing sampling study to the current study?

Receiver Operating Characteristic (ROC) Curve

Estimate and graph an empirical ROC curve along with the 45-degree line for a non informative classifier.

Estimate the area-under-the ROC curve (AUC ROC), the S.E. of the AUC ROC, a lower 95% C.I. for the true AUC ROC, and / or partial AUC ROCs (PAUC ROC) corresponding to a range of values above a false positive rate (FPR) of particular interest. The AUC ROC is the average true positive rate (TPR) taken uniformly over all possible FPRs in the range (0,1).

Identify threshold point(s) that are optimal in some sense. For example, the threshold point with Euclidean distance closest to a perfect predictor, i.e., closest to the point (0,1) in the top left hand corner of the ROC curve graph. Or, identify the point with maximum vertical distance (MVD) away from the 45 degree non informative "chance diagonal" line

running from (0,0) to (1,1) on which TPR=FPR. The Youden Index (YI) identifies that point which maximizes the difference between TPR and FPR. It turns out that MVD is equivalent to YI.

For a (one-tailed) statistical test of the difference between the true ROC curve and the chance diagonal line we can use the sample estimate of the MVD which is the Kolmogorov-Smirnov statistic for non-parametric testing the equality of the two population distribution functions. Or, it may be of interest to test H_0: AUC ROC = 0.5 vs. H_1: AUC ROC > 0.5 using a standardized test statistic referencing N(0,1).

It is likely that the ROC curve will be over fit to the data and the resulting summary statistics will be optimistic. AUC ROC and other summary (and inferential) statistics can be validated with bootstrapping and adjusted accordingly. The data set is too small for data splitting into a training set and test set, and probably too small for k-data-set cross validation except on the order of leave-one-out, k=n.

If a strong case for population normality of the CSF tau/$A\beta_{1\text{-}42}$ ratios can be made, or suitable monotone transformations (Box-Cox) to normality can be found, and the added information is worth the work, the Binormal model for the ROC curve might be used. But extra proof for normality is required as non-normality is notably more serious for ROC curves of individual values than for the more familiar statistical procedures based upon summary statistics like the sample mean. A third alternative is a kernel density method which may require a great deal of iteration.

Comparing ROC Curves

Graph the empirical (or binormal) ROC curves from the two studies simultaneously on the same graph.

The AUCs from the empirical ROCs from the two studies can be compared using the statistic, $T = (AUC_1\text{-}AUC_2)^2 / (s^2_1 + s^2_2)$ which under H_0: is asymptotically distributed as $\chi^2_{(1)}$. Binormal model curves can be compared as well.

The curves can be compared at a given point using tests for comparing two independent proportions. For example, comparing the two TPRs at a fixed FPR. Similarly, the true difference in TPRs can be estimated with the corresponding confidence interval for the true difference. Binormal model analogues exist.

Entire ROC curves can be compared. A non parametric approach tests that the integrated unsigned differences between the misclassification rates is zero. In the Binormal model this reduces to simultaneously testing the null hypothesis of equality of the two pairs of Binormal parameters against the alternative that one or more pairs of Binormal parameters are not equal.

To identify which potions of two ROC curves differ, simultaneous confidence intervals for the true difference in TPRs can be constructed, and then identifying those FPRs for which the CIs exclude zero. Additional information can be found in [3, 10, 11, 12, 13].

Bayesian Updates

Using beta distribution priors from the ongoing sampling study, update the sensitivity and specificity estimates for the CSF tau/$A\beta_{1-42}$ ratio threshold by adding in the binomial results from the current study. The posterior distributions will generate probability statements of interest including credible intervals. Also of interest are the predictive distributions corresponding to sensitivity and specificity for the prodromal study to follow [14, 15].

Additional Exploratory Analyses

More frequentist ROC curve and Bayesian statistical methods including those for ROC curves and threshold values [16, 17] will be considered as the discussion of how the company plans to use the information from both studies matures going forward into the prodromal study.

3.5.3.3 Unplanned Interim Analysis of the Data – Primary Hypothesis # 2

Given the timing of the current study, the ongoing development of a definitive assay, and the timing of the subsequent prodromal study, the recruitment of either or both ADs (n=55) and HE subjects (n=55) may be incomplete (e.g., n=20, 30, or 40) when the prodromal study starts. The data accumulated in the current study may need to be assessed prior to starting the prodromal study.

Sequential Repeated Confidence Intervals

Once the incomplete sample sizes are known, a sequential repeated confidence interval (RCI) strategy will be built planning to estimate both sensitivity and specificity, and the corresponding confidence intervals, at the interim point, and then again at the completion of the study [2].

Bayesian Updates

In addition to the repeated confidence intervals, a Bayesian update of the sensitivity and specificity, and corresponding credible intervals, may be computed. Also of interest are the predictive distributions corresponding to the sensitivity and specificity for the remaining ADs and HEs to be recruited to complete the current study, or projecting beyond that to the prodromal study.

Primary Hypothesis # 1

The unplanned interim sequential RCIs and Bayesian updates were described in terms of Primary Hypothesis # 2. The same approaches can be taken with Primary Hypothesis # 1, provided that the CSF sample collection and the subsequent Tween assay of CSF tau/$A\beta_{1-42}$ ratios as performed by the central lab, can be classified as either a "success" or "failure" for each AD or HE based upon some quality and timeliness criteria.

3.5.3.4 Pharmacogenetics (PGt) studies

Exploratory pharmacogenetics (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Pharmacogenetic studies will be conducted with Biostatistics design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials.

3.5.4 Multiplicity

Primary Hypothesis #2

Planned Analyses: Since the two 95% CIs are independent, together they form a rectangular joint > 90% (0.95*0.95 = 0.9025) confidence region for specificity and sensitivity [3].

Unplanned Interim Analyses: Sequential repeated confidence intervals [2] will be used for both sensitivity and specificity estimation which further accommodates achieving an overall confidence level of 90%.

3.5.5 Sample Size Precision, and Power

Primary Hypothesis #2

Planned Analyses

To calculate power for this study, it was assumed for the CSF tau/$A\beta_{1-42}$ ratio threshold determined from the ongoing sampling study, that the true sensitivity = 0.80 and the true specificity = 0.60. Simulations performed previously by Biometrics Research indicate that 51 AD patients are sufficient to show with .93 power (α=0.05, one-tailed) that the true sensitivity is greater than 0.60. Similarly, with 51 control subjects there is 0.88 power (α=0.05, one-tailed) to show that the true specificity is greater than 0.40. Therefore, the lower bounds on the one-sided CIs observed for sensitivity and specificity should not, with their assigned probabilities, be more than 0.20 below their true value.

The null hypothesis that the sensitivity is $\leq$ 0.60 or that the specificity is $\leq$ 0.40, will be rejected in favor of the alternative that the sensitivity > 0.60 and the specificity is > 0.40, if the hypothesized point (sensitivity=0.60, specificity=0.40) does not lie in the joint >90% confidence region. The power for rejecting the null hypothesis is >0.80 (0.93 x 0.88 = 0.8184).

Unplanned Interim Analyses

The sample sizes for ADs and HEs will not be known until the interim analyses become necessary. Assuming that the true sensitivity =0.80 and that either 20, 30, or 40 ADs have completed at the time the unplanned analysis becomes necessary, then there is

approximately 0.90 power (α=0.05, one-tailed) to demonstrate that the true sensitivity is greater than 0.49, 0.53, and 0.58, respectively. The corresponding values for an assumed specificity in HEs of 0.60 are 0.25, 0.33, and 0.36. The overall power (sensitivity and specificity combined) is approximately 0.81.

3.6 LABELING, PACKAGING, STORAGE, DISPENSING, AND RETURN OF CLINICAL SUPPLIES

There is no study medication as part of this clinical trial.

3.7 DATA MANAGEMENT

Information regarding Data Management procedures for this protocol will be provided by the SPONSOR.

3.8 BIOLOGICAL SPECIMENS

Information regarding biological specimens for this protocol will be provided by the SPONSOR.

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4. ADMINISTRATIVE AND REGULATORY DETAILS

4.1 CONFIDENTIALITY

4.1.1 Confidentiality of Data

For Studies Conducted Under the U.S. IND

Particular attention is drawn to the regulations promulgated by the Food and Drug Administration under the Freedom of Information Act providing, in part, that information furnished to clinical investigators and Institutional Review Boards will be kept confidential by the Food and Drug Administration only if maintained in confidence by the clinical investigator and Institutional Review Board.

For All Studies

By signing this protocol, the investigator affirms to the SPONSOR that information furnished to the investigator by the SPONSOR will be maintained in confidence and such information will be divulged to the Institutional Review Board, Ethics Review Committee, 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.

4.1.2 Confidentiality of Subject/Patient Records

For All Studies

By signing this protocol, the investigator agrees that the SPONSOR (or SPONSOR representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject/patient agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject/patient will be identified by unique code only; full names/initials will be masked prior to transmission to the SPONSOR.

For Studies Conducted Under the U.S. IND

By signing this protocol, the investigator agrees to treat all patient data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations, including all applicable provisions of the Health Insurance Portability and Accountability Act and its implementing regulations, as amended from time to time ("HIPAA").

4.1.3 Confidentiality of Investigator Information

For All Studies

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site

personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number, and email address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- other professional documentation.

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

For Multicenter Studies
In order to facilitate contact between investigators, the SPONSOR may share an investigator's name and contact information with other participating investigators upon request.

4.2 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 Good Clinical Practice; 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 Merck, is attached.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/ Independent Ethics Committee review, and regulatory agency inspection of trial-related documents and procedures and provide for direct access to all study-related source data and documents.

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

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Clinical Practice standards and applicable federal, state, and local laws, rules and regulations; and, for each subject/patient participating in the study, provide all data, and upon completion or termination of the clinical study submit any

other reports to the SPONSOR as required by this protocol or as otherwise required pursuant to any agreement with the SPONSOR.

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

International Conference of Harmonization Good Clinical Practice guidelines (Section 4.3.3) recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

According to European legislation, a SPONSOR must designate a principal or coordinating investigator (CI) to review the report (summarizing the study results) and confirm that to the best of his/her knowledge the report accurately describes conduct and results of the study. The SPONSOR may consider one or more factors in the selection of the individual to serve as the CI (e.g., thorough understanding of clinical trial methods, appropriate enrollment of subject/patient cohort, timely achievement of study milestones, availability of the CI during the anticipated review process).

The investigator will promptly inform the SPONSOR of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on clinical studies by any court or regulatory agency 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.

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

4.3 COMPLIANCE WITH FINANCIAL DISCLOSURE REQUIREMENTS

By signing this protocol, the investigator agrees to provide to the SPONSOR accurate financial information to allow the SPONSOR to submit complete and accurate certification and disclosure statements as required by U.S. Food and Drug Administration regulations (21 CFR Part 54). The investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. This requirement also extends to subinvestigators. The investigator also consents to the transmission of this information to Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

4.4 QUALITY CONTROL AND QUALITY ASSURANCE

By signing this protocol, the SPONSOR agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written SOPs to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

4.5 COMPLIANCE WITH INFORMATION PROGRAM ON CLINICAL TRIALS FOR SERIOUS OR LIFE THREATENING CONDITIONS

Under the terms of The Food and Drug Administration Modernization Act (FDAMA), the SPONSOR of the study is solely responsible for determining whether the study is subject to the requirements for submission to the Clinical Trials Data Bank, http://clinicaltrials.gov/. Merck, as SPONSOR of this study, will review this protocol and submit the information necessary to fulfill this requirement. Merck entries are not limited to FDAMA mandated trials. Merck's voluntary listings, beyond those mandated by FDAMA, will be in the same format as for treatments for serious or life-threatening illnesses. Information posted will allow patients to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligation under FDAMA is that of the SPONSOR and agrees not to submit any information about this study to the Clinical Trials Data Bank.

4.6 PUBLICATIONS

This is an exploratory study in normal volunteers* and is not intended for publication, because such data are used primarily to guide development and design of possible future confirmatory clinical trials. However, if medically important new information or data are obtained in this study, the SPONSOR will work with the investigator(s) to publish the data appropriately. In that case, the SPONSOR must have the opportunity to review all proposed abstracts, manuscripts, or presentations regarding this study 60 days prior to submission for publication/presentation. Any information identified by the SPONSOR as confidential must be deleted prior to submission. SPONSOR review can be expedited to meet publication timelines.

*For vaccine trials, this includes initial Phase I trials where the primary objective is to gain information on the safety and tolerability of the vaccine, even if immunogenicity data are also acquired.

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Product: Non-Product 3
Protocol/Amendment No.: 261-00

6. APPENDICES

6.1 LABORATORY SAFETY TEST

Hematology	Chemistry	Urinalysis
Basophils	Albumin	Blood
Eosinophils	ALT (SGPT)	Glucose
Hematocrit	AST (SGOT)	Ketones
Hemoglobin	Bicarbonate	pH
Lymphocytes	Blood urea nitrogen (BUN)	Protein
Monocytes	Calcium	Specific gravity
Neutrophils	Chloride	Culture if indicated
Platelets	Creatinine	
RBC	Folate [b]	
WBC	Glucose	
	Homocysteine and methylmelonic acid [a, b]	
	Inorganic phosphorus	
	Potassium	
	Sodium	
	T4	
Other	Total Bilirubin	
PT (INR)	Total protein	
PTT	TSH [b]	
RPR	Vitamin B12 [a]	
Hep B/HIV	βhCG	

[a] Homocysteine and methylmelonic acid should only be measured if folate or vitamin B12 is below normal range

[b] TSH should only be measured if T4 is below normal range

6.2 ALGORITHM FOR ASSESSING OUT OF RANGE LABORATORY VALUES

For all laboratory values obtained at prestudy (screening) visit evaluation:

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

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

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

   1. The subject may be excluded from the study;

   2. The subject may be included in the study if the abnormal value(s) is not clinically significant (NCS) (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).

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

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

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

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

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

6.3 THE NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISEASES AND STROKE/ALZHEIMER'S DISEASE AND RELATED DISORDERS ASSOCIATION (NINCDS-ADRDA) CRITERIA FOR PROBABLE AD

Excerpt from [5]

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

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

II. The diagnosis of Probably Alzheimer's disease is supported by:

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

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

- plateaus in the course of progression of the illness;
- associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders and weight loss;
- other neurologic abnormalities in some patients, especially with more advances disease and including motor signs such as increased muscle tone, myoclonus or gait disorder;
- seizures in advanced disease; and
- CT normal for age.

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

- Sudden, apoplectic onset;
- Focal neurologic findings such as hemiparesis, sensory loss, visual field deficits and incoordination early in the course of the illness; and
- Seizures of gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of possible Alzheimer's disease:

- May be made on the basis of the dementia syndrome, in the absence of other neurologic psychiatric or systemic disorders sufficient to cause dementia and in the presence of variations, in the onset in the presentation or in the clinical course;
- May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia; and
- Should be used in research studies when a single, gradually progressive sever cognitive deficit is identified in the absence of other identifiable causes.

VI. Criteria for diagnosis of Definite Alzheimer's disease are:

- The clinical criteria for probably Alzheimer's disease and histopathologic evidence obtained from a biopsy or autopsy

VII. Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:

- Familial occurrence;
- Onset before age 65;
- Presence of trisomy-21; and
- Coexistence of other relevant conditions such as Parkinson's disease

6.4 DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS, 4TH EDITION, TEXT REVISION (DSM-IV-TR) CRITERIA FOR 294.1X DEMENTIA OF THE ALZHEIMER'S TYPE

A. The development of multiple cognitive deficits manifested by both

1. memory impairment (impaired ability to learn new information or to recall previously learned information)

2. one (or more) of the following cognitive disturbances:

a) aphasia (language disturbance)

b) apraxia (impaired ability to carry out motor activities despite intact motor function

c) agnosia (failure to recognize or identify objects despite intact sensory function)

d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)

B. The cognitive deficits in Criteria A1 and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.

C. The course is characterized by gradual onset and continuing cognitive decline.

D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following:

1. other central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerbrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor)

2. systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B12 or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection

3. substance-induced conditions

E. The deficits do not occur exclusively during the course of a delirium

F. The disturbance is not better accounted for my other Axis I disorder (e.g., Major Depressive Disorder, Schizophrenia).

6.5 COLLECTION AND MANAGEMENT OF SPECIMENS FOR FUTURE BIOMEDICAL RESEARCH

6.5.1 Scope of Future Biomedical Research

The DNA specimen(s) collected in the current trial will be used to study various causes for how subjects may respond to a drug. The DNA specimen(s) will be stored to provide a resource for future studies conducted by Merck focused on the study of biomarkers responsible for how a drug enters and is removed by the body, how a drug works, other pathways a drug may interact with, or other aspects of disease.

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, 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 Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

6.5.2 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 response.[2]

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

6.5.3 Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-study.

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1 National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker

2 International Conference on Harmonization: Definitions For Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all subjects 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 subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens.

Subjects are not required to participate in the Future Biomedical Research sub-study in order to participate in the main trial.

Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced to any specimens, test results, or medical information once the specimens have been rendered de-identified. Subjects who decline to sign the Future Biomedical Research informed consent will not have the specimen collected nor will they be discontinued from the main study.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

Each informed consent approved by an ethics committee is assigned a unique tracking number. The tracking number on this document will be used to assign specimen permissions for each specimen into the Entrusted Keyholder's Specimen Database.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of both consent and acquisition of Future Biomedical Research specimens will be captured in the electronic Case Report Forms (eCRFs). Reconciliation of both forms will be performed to assure that only appropriately-consented specimens are used for this sub-study's research purposes. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Blood specimens for DNA isolation will usually be obtained at a time when the subject is having blood drawn for other study purposes. Specimens like tissue and bone marrow will usually be obtained at a time when the subject is having such a procedure for clinical purposes.

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

6.5.4 Confidential Subject 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 subject' 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 subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, Merck has developed secure policies and procedures. All specimens will be de-identified as described below.

At the clinical site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

This first code will be replaced with a second code at a Merck designated storage/lab facility. The second code is linked to the first code via a second key. The specimen is now double coded. Specimens with the second code are sometimes referred to as de-identified specimens. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code. Access to both keys would be needed to link any data or specimens back to the subject's identification.

The second code is stored separately from the first code and all associated personal specimen identifiers. A secure link, the second key, will be utilized to match the second code to the first code to allow clinical information collected during the course of the study to be associated with the specimen. This second key will be transferred under secure procedures by the Merck designated facility to an Entrusted Keyholder at Merck. The second code will be logged into the primary biorepository database at Merck and, in this database, this identifier will not have identifying demographic data or identifying clinical information (i.e., race, sex, age, diagnosis, lab values) associated with it. The specimen will be stored in a designated biorepository site with secure policies and procedures for specimen storage and usage.

The second key can be utilized to reconstruct the link between the results of future biomedical research and the clinical information, at the time of analysis. This linkage would not be possible for the scientist conducting the analysis, but can only be done by the Merck Entrusted Keyholder under strict security policies and procedures. The Merck Entrusted Keyholder will link the information and then issue a de-identified data set for analysis. The only other circumstance by which future biomedical research data would be directly linked to the full clinical data set would be those situations mandated by health authorities (e.g., EMEA, FDA), whereby this information would be directly transferred to the health authority.

6.5.5 Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. However, exploratory analyses will not be conducted under the highly validated conditions usually associated with regulatory approval of diagnostics. The scope of research performed on these specimens is limited to the investigation of the variability in biomarkers that may correlate with a clinical phenotype in subjects.

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-study. Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

6.5.6 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by writing to the principal investigator for the main study. If medical records for the main study are still available, the Investigator will contact MERCK using the designated mailbox PPD and a form will be provided by MERCK to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from MERCK to the investigator confirming the destruction. It is the responsibility of the Investigator to inform the patient of completion of destruction. Any analyses in progress at the time of request for 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 (e.g., if the investigator is no longer required by regulatory agencies to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the patient's personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

6.5.7 Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from acquisition. Specimens may be stored for longer if a regulatory or governmental agency 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 site will be shipped to a central laboratory and then shipped to the Merck 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 Merck policies and procedures and this destruction will be documented in the biorepository database.

6.5.8 Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-study will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized sponsor 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 in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These data are collected for future biomedical research purposes only as specified in this sub-study will not be used for any other purpose.

6.5.9 Reporting of Future Biomedical Research Data to Subjects

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to study participant. Some guidelines advocate a proactive return of data in certain instances. No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database maintained by Merck on subjects. Principle reasons not to inform or return results to the subject include: lack of relevance to subject health, limitations of predictive capability, concerns of misinterpretation, and absence of good clinical practices standards in exploratory research typically used for diagnostic testing.

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

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

6.5.10 Gender, Ethnicity, and Minorities

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

6.5.11 Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main study.

Merck has developed strict security, policies and procedures to address subject 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.

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

6.5.12 Self-Reported Ethnicity

Subjects who participate in future biomedical research will be asked to provide self-reported ethnicity. Subjects who do not wish to provide this data may still participate in future biomedical research.

6.5.13 Questions

Any questions related to the future biomedical research should be e-mailed directly to PPD

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Protocol/Amendment No.: 261-00

7. ATTACHMENTS

Merck & Co., Inc. Code of Conduct for Clinical Trials

Pharmacogenomics Informational Brochure for IRBs/IECs & Investigational Site Staff

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Study Conduct

1. Study Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Patient Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. DNA Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

04KYDZ

Pharmacogenomics Informational Brochure

for IRBs/IECs & Investigational Site Staff

INDUSTRY

I-PWG

PHARMACOGENOMICS WORKING GROUP

04KYDZ

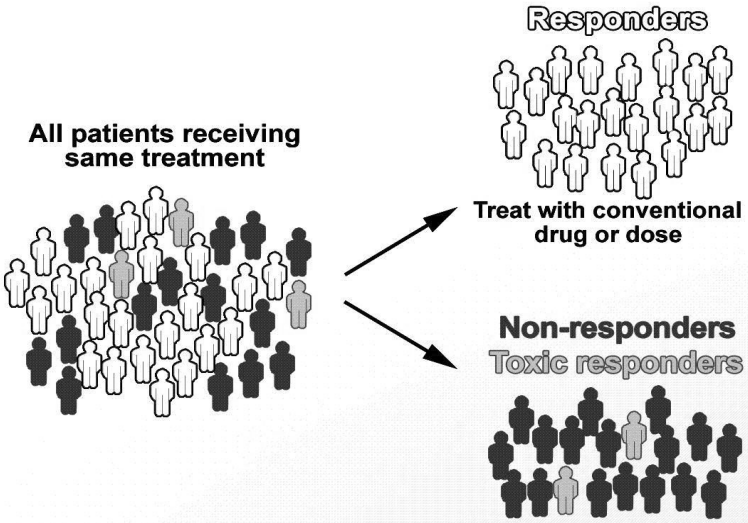
This Informational Brochure is intended for IRBs/IECs & Investigational Site Staff. The brochure was developed to address issues relevant to DNA collection and research in the context of pharmaceutical drug development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

What is DNA and What is Pharmacogenomics?

The cells of the body contain **deoxyribonucleic acid** (**DNA**). DNA is inherited, and carries a code (in the form of **genes**), which determines physical appearance and other personal features. In a process called gene transcription, DNA is copied into a related molecule, ribonucleic acid (RNA), before ultimately being translated into proteins, which determine cellular function. Naturally-occurring variation in DNA is a major determinant of differences among people. This variation, referred to as **genetic polymorphism**, occurs both within genes and outside of genes throughout the entire **human genome**. This variation partly explains why some people develop certain diseases and others do not, why some people respond better than others to certain drugs, and why some people develop side effects while others do not.

Pharmacogenomics (PGx) is a branch of science that uses genetic/genomic information to better understand why people respond differently to drugs. The terms **pharmacogenomics** and **pharmacogenetics** are often used interchangeably, although pharmacogenetics generally refers to the study of DNA, while pharmacogenomics is a broader term encompassing the study of both DNA and RNA[1], and generally on a larger scale. Pharmacogenomic research is different from **genetic testing** done for the purpose of diagnosing a person with a certain disease or for risk for developing a certain disease (e.g., genetic testing for Huntington's Disease). PGx focuses on genetic variability that affects response to drugs. This primarily occurs through pathways related to drug metabolism, drug mechanism of action, disease etiology or subtype, and adverse events. PGx overlaps with **disease genetics** research since different disease subtypes can respond differently to drugs.



Why is Pharmacogenomics Important?

PGx is one approach to explore whether a drug will be useful or harmful in certain people. By identifying genetic polymorphisms that are associated with drug efficacy and safety, PGx is allowing for more individualized drug therapies based on the genetic makeup of patients. This is sometimes referred to as **personalized medicine**. By better understanding diseases at the molecular level, PGx is opening opportunities for the discovery of novel drugs.

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PGx has the overarching goal of developing safer, more effective drugs, and ensuring that patients receive the correct dose of the correct drug at the correct time.

How is Pharmacogenomics Being Used in Drug Development?

PGx is increasingly becoming a core component of drug development programs. By using PGx to determine how drugs work differently in subgroups of patients, drug developers are making better decisions about which drugs to develop and how best to develop them. Technologies are now available to simultaneously analyze over 1 million genetic polymorphisms in the human genome. This is allowing for the identification of novel genetic markers of drug response and of disease in absence of pre-existing knowledge of the involvement of specific pathways.

PGx research is currently being used in drug development to:

- Explain variability in response among subjects in clinical trials
- Address emerging clinical issues, such as unexpected adverse events
- Determine eligibility for clinical trials (pre-screening) to optimize trial design
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of adverse events
- Better understand the mechanism of action or metabolism of new and existing drugs
- Provide better understanding of disease mechanisms
- Allow physicians to prescribe the right drugs at the optimal dose for individual patients

Pharmacogenomics Already a Reality in Drug Labels

A number of drugs now have instructions on their labels either recommending or requiring a PGx test when prescribing a drug or when making dosing decisions. A well-known example is the anti-coagulant drug *warfarin*. The drug label for warfarin now includes a recommended PGx test to minimize the risk of excessive bleeding (US label). There are currently three categories of PGx information in drug labels according to the FDA:

i) tests **required** for prescribing

ii) tests **recommended** when prescribing

iii) PGx information **for information only**.

For a current list of examples of how PGx is impacting drug labeling see:

http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm

DNA Samples from Clinical Trials An Invaluable Resource

Adequate sample sizes and high-quality clinical data are key to advancements in the field of PGx. Drug development programs are therefore an invaluable resource and a unique opportunity for highly productive research in PGx. Although PGx is a rapidly evolving branch of science, the complexities of the genetic code are only beginning to be understood. As scientific discoveries continue to be made, samples collected today will become a valuable resource

for future research. This may lead to the future development of new drugs that are better targeted to certain individuals and to disease subtypes.

For these reasons, it is vital to systematically collect DNA samples across all centers recruiting subjects into clinical trials that include a PGx component (where local regulations permit). Consent for storage of samples for future research should also be obtained if maximum benefit is to be derived from DNA samples donated by subjects. The scope of the research that may be performed both during the trial and in the future should be clearly defined in the informed consent form.

Informed Consent

Policies and regulations for legally effective informed consent vary on national, state, and local levels. There currently are no internationally recognized regulations that dictate the basic elements of informed consent for PGx research. The I-PWG has published an article on the elements of informed consent to be considered in PGx research studies[2]. These elements build upon existing basic elements of informed consent for clinical research on human subjects[3].

Return of Genomic Research Results to Study Subjects

Policies for the return of genomic results to study subjects vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of PGx research results to study subjects. These include i) the conditions under which genomic results were generated (i.e., research laboratory environment versus accredited diagnostic laboratory), ii) whether the results will have an impact on patient medical care, iii) whether genetic counseling is necessary, and iv) international, national, and local guidelines, policies, legislation, and regulations regarding subjects' rights to access data generated on them. These considerations are addressed in detail in Renegar et al. 2006[4].

Privacy, Confidentiality, and Patient Rights

An issue that is generally perceived to be of relevance to clinical genetic research is the risk associated with inadvertent or intentional disclosure and misuse of genetic data. Although coded specimens generally have been considered adequate to protect patient privacy in most clinical development, companies and other institutions involved in PGx research have historically applied a variety of additional safeguards that can be used alone, or in combination, to further minimize the potential risk of disclosure and misuse of genetic data. These include:

i) Sample Labeling

DNA samples and corresponding clinical data can be labeled in several ways to achieve different levels of patient privacy and confidentiality. Definitions of labeling methods are provided in the glossary and are described in greater detail in the ICH Guidance E15[1]. It is important to recognize that there is a trade-off between the level of patient privacy protection and the ability to perform actions related to withdrawal of consent, data return, clinical monitoring, subject follow-up, and addition of new data (see Table 1)[1]. The *Identified* and *Anonymous* labeling categories described in the table are generally not applicable to pharmaceutical clinical trials.

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Table adapted from ICH Guidance E15

Sample Coding Category		Link Between Subject's Personal Identifiers and Genomic Biomarker Data	Traceability back to the Subject (Actions Possible, Including e.g., Sample Withdrawal or Return of Individual Genomic Results at Subject's Request	Ability to Perform Clinical Monitoring, Subject Follow-up, or Addition of New Data	Extent of Subject's Confidentiality and Privacy Protection
Identified		Yes (Direct) Allows for Subjects to be Identified	Yes	Yes	Similar to General Healthcare Confidentiality and Privacy
Coded	**Single**	Yes (Indirectly) Allows for Subjects to be Identified (via Single, Specific Coding Key)	Yes	Yes	Standard for Clinical Research
	Double	Yes (Very Indirectly) Allows for Subjects to be Identified (via the Two Specific Coding Keys)	Yes	Yes	Added Privacy and Confidentiality Protection over Single Code
Anonymized		No Does not Allow Subject to be Re-Identified as the Coding-Key(s) Have Been Deleted	No	No	Genomic Data and Samples no Longer Linked to Subject as Coding Key(s) have been Deleted
Anonymous		No – Identifiers Never Collected and Coding Keys Never Applied. Does not Allow for Subjects to be Identified	No	No	Genomic Data and Samples Never Linked to Subject

ii) Separation of Data and Restricted Access

- Maintaining PGx-related documentation separate from other medical records.
- Restricting access to data and samples by means of password-protected databases and locked sample storage facilities.

PGx studies in pharmaceutical development are generally conducted in research laboratories that are not accredited diagnostic laboratories. Therefore, PGx research data usually cannot be used to make clinically meaningful or reliable decisions about a subject's health or health risks. Furthermore, confidentiality protections described above serve to guard against inappropriate disclosure of these data. For these reasons, the potential risk to a subject's employment or health/life insurance is considered to be minimal. The measures taken to protect subjects against reasonably foreseeable risks should be addressed in the informed consent form[2].

iii) Legislation on Genetic Discrimination

Many countries and regions have enacted legislation to protect individuals against discrimination based on their genetic information. For example, the USA Genetic Non-discrimination Act (GINA)[5, 6] serves to protect patients against health insurance and employment discrimination based on an individual's genetic make-up. Legislation continually evolves based on social, ethical, and legal considerations. A list of examples is periodically updated on the I-PWG website: **http://www.i-pwg.org**

Country-Specific Laws and Regulations on DNA Collection

DNA sampling in clinical trials is straightforward in most jurisdictions. However, some countries have specific laws and regulations regarding collection, labeling, storage, export, return of results, and/or use of DNA samples. Processes for the collection of DNA samples should always adhere to the regulations of the country/region in which those samples are collected. Efforts are currently underway toward improving harmonization and standardization of regulations and practices applicable to collection of DNA samples. However, it may be well into the future before there is consensus across nations. Because country-specific local and regional laws and regulations continually evolve, it is advisable to regularly verify these laws and regulations for the jurisdiction in which approval for DNA collection is being given.

Regulatory Authorities

The use of PGx information to improve the risk:benefit profile of drugs is increasingly being encouraged by regulatory health authorities. Authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development. A significant number of regulatory guidances and concept papers have already been issued[1, 3, 7-18], and are available through: **http://www.i-pwg.org**. DNA sample collection has become a key component of clinical development. It is anticipated that regulatory authorities eventually may require relevant PGx data with drug submissions[19].

Where to Get More Information

Several expert organizations are helping to advance the adoption of PGx in clinical development and in medical care. A vast array of educational resources related to PGx that cater to health care professionals, IRBs/IECs, scientists, and patients have been created and are publicly available. Many of these organizations and resources are available through the I-PWG website: **http://www.i-pwg.org**.

What is the Industry Pharmacogenomics Working Group (I-PWG)?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in PGx research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of PGx research for key stakeholders. The I-PWG interacts with regulatory authorities and policy groups to ensure alignment. More information about the I-PWG is available at: **http://www.i-pwg.org**.

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Glossary

Identified Data and Samples: Identified data and samples are labeled with personal identifiers such as name or identification numbers (e.g., social security or national insurance number). The use of identified data and samples allows for clinical monitoring and subject follow-up and are generally not considered appropriate for purposes of clinical trials in drug development. (Not generally applicable to PGx in pharmaceutical clinical trials).

Coded Data and Samples: Coded data and samples are labeled with at least one specific code, and do not carry any personal identifiers.

> ***Single-Coded Data and Samples:*** are usually labeled with a single specific code. It is possible to trace the data or samples back to a given individual with the use of a single coding key.

> ***Double-Coded (De-Identified) Data and Samples:*** are initially labeled with a single specific code and do not carry any personal identifiers. The data and samples are then relabeled with a second code, which is linked to the first code via a second coding key. It is possible to trace the data or samples back to the individual by the use of both coding keys. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code.

Anonymized Data and Samples: Anonymized data and samples are initially single or double coded but the link between the subjects' identifiers and the unique code(s) is subsequently deleted. Once the link has been deleted, it is no longer possible to trace the data and samples back to individual subjects through the coding key(s). Anonymization is intended to prevent subject re-identification.

Anonymous Data and Samples: Anonymous data and samples are never labeled with personal identifiers when originally collected, nor is a coding key generated. Therefore, there is no potential to trace back genomic data and samples to individual subjects. Due to restrictions on the ability to correlate clinical data with such samples, they are generally of little use to PGx research. (Not generally applicable to PGx in pharmaceutical clinical trials).

References

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Product: Non-Product 1
Protocol/Amendment No.: 261-00

8. SIGNATURES

8.1 SPONSOR'S REPRESENTATIVE

TYPED NAME	SIGNATURE	DATE

8.2 INVESTIGATOR

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 (including other manuals and documents referenced from this protocol); deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in the SAFETY MEASUREMENTS section of this protocol. I also agree to handle all clinical supplies provided by the SPONSOR and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

TYPED NAME	SIGNATURE	DATE