Protocol Number: CN156018
IND Number: 77,402
Ex-US Non-IND
EUDRACT Number 2009-010067-16
Date: 03-Mar-2009
Revised Date: 20-Dec-2012

Clinical Protocol CN156018

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Tolerability, Pharmacodynamic and Pharmacokinetic Effects of BMS-708163 in the Treatment of Patients with Prodromal Alzheimer's Disease

Revised Protocol Number: 10
Incorporates Amendment: 16

Study Director/Central Medical Monitor

Vlad Coric, MD
Group Director
Global Clinical Research, Neuroscience

5 Research Parkway
Wallingford, CT 06492

Telephone (office): 203-677-3533

Fax: 203-677-7695

Protocol Manager

Judith Braga, MPH
Senior Protocol Manager
Global Clinical Operations & Strategy

5 Research Parkway
Wallingford, CT 06492

Telephone (office): 203-677-6659

Fax: 203-677-7871

24-hr Emergency Telephone Number
USA: 1-866-470-2267
International: +1-248-844-7390

Bristol-Myers Squibb Research and Development
Neuroscience Clinical Research and Development

Avenue de Finlande 4
B-1420 Braine-l'Alleud, Belgium

5 Research Parkway
Wallingford, CT 06492

2 STUDY OBJECTIVES

2.1 Primary Objective

To assess the long term safety and tolerability of BMS-708163 in patients with prodromal Alzheimer's Disease.

2.2 Secondary Objectives

To assess the predictive value of CSF biomarkers (Aβ40, and Aβ42, total Tau, total Tau/Aβ42 ratio, and phosphorylated Tau) on progression to dementia.

2.3 Exploratory Objectives

1) To explore drug effects on progression to dementia (based on confirmed progression using DSM-IV criteria)

a) To explore effects of BMS-708163 on brain atrophy rate as measured by volumetric MRI

b) To explore and prospectively characterize effects the Clinical Dementia Rating scale (including the CDR-Sum of Boxes score and CDR global score), an instrument designed to measure the severity of cognitive symptoms in daily life, as part of the natural course (in placebo patients) and potential impact of BMS-708163

c) To explore the correlation of APOE status with BMS-708163 pharmacodynamic (PD) effects (such as on biomarkers and cognition)

d) To explore Aβ42 CSF Screening cut-off value of > 200 pg/mL versus < 200 pg/mL and Total Tau/AB42 ratio ≥ 0.39 with regard to progression rates and biomarker changes in both the randomized and the non-randomized, observational cohort of subjects

e) To explore the pharmacodynamic effects of BMS-708163 on CSF biomarkers linked to mode of action (Aβ38, Aβ40, Aβ42), and putative biomarkers of neurodegeneration (total Tau, phosphorylated Tau) and lipid peroxidation (isoprostanes) in AD

f) To explore the pharmacodynamic effects of BMS-708163 on Cognition as assessed by an Executive Function Test Battery and the ADAS-cog

g) To explore the pharmacodynamic effects of BMS-708163 on Function in daily living as assessed with the Alzheimer's disease Collaborative Study - Activities of Daily Living scale (ADCS-MCI-ADL)

h) To explore the pharmacodynamic effects of BMS-708163 on progression on the Global Clinical Dementia Rating (CDR global) (ie, progression to a global score of 1)

i) To explore effects of BMS-708163 on brain amyloid content as measured via PET-amyloid imaging (AV-45) in a subset of subjects at specified sites

j) To explore the pharmacodynamic effects of BMS-708163 on the subject-reported Outcomes in Cognitive Impairment (PROCOG), an instrument designed to assess severity of impairment and impact on subjects

k) To assess Notch-mediated (safety related) effects of BMS-708163 on:
   - TFF3 plasma concentrations and its association with gastrointestinal safety signals
   - Lymphocyte mRNA levels of HES-1 and its association with clinical safety signals
   - The immune system (lymphocyte subpopulations; immunoglobulin serum levels)

2) To characterize pharmacokinetics (PK) and its relationship with pharmacodynamic (PD) effects:
   - Characterize plasma exposure of BMS-708163 and variability in a population with Alzheimer's disease
   - Characterize the relationship between BMS-708163 exposure and CSF biomarker response
   - Explore the relationships between BMS-708163 exposure and cognitive scores (ADAS- cog and others)

– Identify the source of exposure variability, including the correlation between polymorphisms of CYP enzymes (eg, CYP2C9 and CYP2C19) and exposures

3 ETHICAL CONSIDERATIONS

3.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s).

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

Systems with procedures that assure the quality of every aspect of the study will be implemented.

3.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to subjects. The investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates.

The investigator or sponsor should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

3.3 Informed Consent

Investigators must ensure that subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from every subject or, in those situations where consent cannot be given by subjects, their legally acceptable

representative, prior to clinical study participation, including informed consent for any screening procedures conducted to establish subject eligibility for the study.

Patients are required to have reliable study partners. A reliable study partner is defined as person who has a minimum of approximately 5 hours/week of direct contact with the study participant and who, in the judgment of the investigator is able to fulfill their study obligations (including being able to reliably describe and assess changes in the subject's condition).

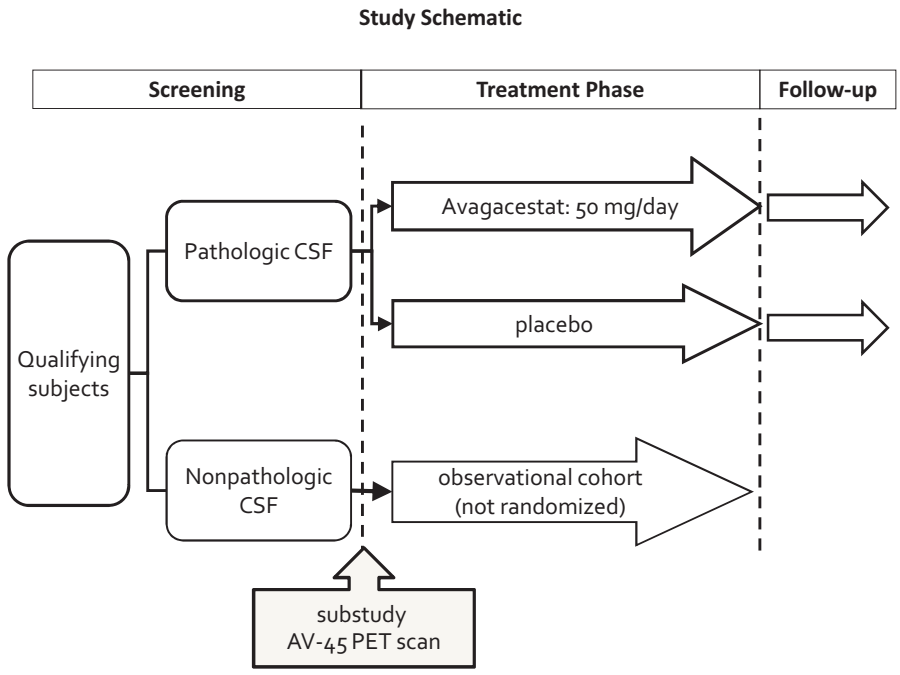
The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

Appendix 1 contains BMS procedures on obtaining informed consent from subjects, or, in those situations where consent cannot be given by subjects, their legally acceptable representative prior to participating in a clinical study. Procedures are described for all subjects, including those who are unable to give informed consent. The relevant procedures must be used whenever they are applicable (see subject selection criteria in Sections 4.2.1 and 4.2.2).

4 INVESTIGATIONAL PLAN

4.1 Study Design and Duration

Figure 4.1-1: Study Schematic



Due to the early termination of this study, the duration of study treatment and performance of the protocol specified termination procedures will not be completed according to the design of the

protocol as previously described. All subjects still receiving study medication at the time of study termination by sponsor will be contacted by the site promptly, instructed to stop dosing, and will be asked to return for an End of Treatment a (EOT) Visit. When the data for that EOT visit has been entered into the EDC system, the treatment code will be provided to the study site. Subjects treated with avagacestat will be scheduled for the Post Treatment/Study Termination Safety Follow-up Visits (to occur 4 Weeks, 12 Weeks, and 24 Weeks after last dose). Subjects who were randomized to the placebo arm, and those enrolled in the observational cohort will be advised of their treatment group and told that no further assessments are required.

Avagacestat-treated subjects should be scheduled for a 4 Week, 12 Week, and 24 Week Post Treatment Safety Follow-up Visit as outlined in Table 6.1-4. All attempts should be made to complete the three Post Treatment/Study Termination Safety Follow-up Visits.

Avagacestat treated subjects participating in the long-term safety follow-up phase **for 12 weeks or less** should be scheduled for a 12 Week Post Treatment/Study Termination Safety Follow-up Visit, as well as for a 24 Week Post Treatment/Study Termination Safety Follow-up Visit for a comprehensive skin examination by a dermatologist (or dermatologic physician's assistant in the United States);

Avagacestat-treated subjects participating in the long-term safety follow-up phase **for greater than 12 weeks** should only be scheduled to return for the 24 Week Post Treatment/Study Termination Safety Follow-up Visit for a comprehensive skin examination by a dermatologist (or dermatologic physician's assistant in the United States).

Additionally all subjects who previously discontinued from this study (ie, those who did not participate in the long-term follow-up) but were exposed to greater than one month (31 days) of treatment with avagacestat should be contacted by the site and scheduled to complete the 24 Week Post Treatment/Study Termination Follow-up Visit for a comprehensive skin examination by a dermatologist (or dermatologic physician's assistant in the United States), irrespective of whether they received. a comprehensive skin examination with a dermatologist (or dermatologic physician's assistant in the United States) at the end of study treatment.

The study is a multi-center, randomized, double-blind, 2-arm, placebo-controlled, parallel-group study in patients with prodromal Alzheimer's disease to evaluate safety, tolerability, pharmacodynamic and pharmacokinetic effects of once-daily dosing of BMS-708163 for a minimum of 104 weeks (refer to Study Schematic in Figure 4.1-1 above).

The treatment period for the study will be a minimum of 104 weeks (2 years). Randomized subjects may continue in the study beyond 104 weeks of treatment (up to an estimated maximum of 220 weeks of treatment) until the last randomized subject has had the opportunity to receive study medication for approximately 104 weeks. Thus, given the recruitment period of approximately 27 months, the overall duration of study treatment is expected to last between 104 and 220 weeks for a given subject. The study treatment phase will end once the last randomized subject has completed approximately 104 weeks of treatment (estimated to occur by September, 2013). All subjects still receiving study medication at the time last patient last

treatment is determined will end treatment and be followed in the Safety Follow-up Visits (4 Weeks and 12 Weeks post end of treatment visit; refer to Section 6.1.1.7).

After assessments of eligibility during the maximum 75 day screening period, subjects will undergo baseline safety and PD assessments. In a subset of subjects, at selected centers, subjects may be consented for 24-hour intensive PK assessments. In another subset of sites, subjects may be consented for PET imaging assessments at pre-specified visits (delineated in a separate, site-specific amendment).

All subjects will be randomly assigned in a double-blind manner to one of the following treatment groups: placebo or 50 mg BMS-708163 once daily. Treatment allocation will be balanced by symptomatic co-medication (ChEI): yes/no; Apolipoprotein E (APOE) Status (yes+/no-), consent for PET Imaging (yes/no) and consent for intensive PK assessments (yes/no).

All subjects will be treated with 50 mg during the study. Downward titration to 25 mg/day of BMS-708163 based upon the investigator's clinical judgment will only be allowed to manage limiting adverse events that emerge during the study. It is recommended that if down-titration does occur, the investigator consider a re-challenge to the highest tolerated dose for the subject to maximize Aβ reductions. If the investigator does not attempt to re-challenge to the highest-tolerated dose, the investigator should contact the BMS medical monitor with the clinical rationale for not re-challenging at the higher dose. For the purposes of down-titration for tolerability issues, a dose range of 25 mg - 50 mg per day will be allowed during the treatment phase. A low dose of 25 mg per day is estimated to provide approximately > 10% Aβ reduction, a level of reduction that may still provide a potentially meaningful reduction in brain Aβ levels

All subjects will have trough PK assessments starting at the Week 2 visit and at all subsequent visits during the treatment period. An additional post-dose PK assessment will be completed at selected visits. At the time of CSF sample collection, both a blood and CSF sample will be collected for plasma and CSF PK analysis. These sample collections are outlined, in the Time & Events Schedule. A subset of subjects, at selected sites, will also complete one intensive 24-hour PK assessment on a day after they have been on treatment for 6 weeks and at a stable dose for at least two weeks (see Section 6.5.5.1). Safety and PD assessments will be performed as outlined in the Time & Events Schedule (see Section 6.1).

Subjects who do not meet the CSF inclusion criteria (CSF Aβ42 < 200 pg/mL or Total Tau/Aβ42 ratio of ≥ 0.39) but otherwise fulfill the study inclusion criteria may continue to be followed for rating scale visits but will not be randomized to any treatment arm. Given the projected CSF Aβ42 Screen Failure rate of 50%, it is estimated that approximately 100 subjects will enter the non-randomized observational group. Subjects in this non-randomized observational cohort will serve to provide prospectively collected comparison data regarding CSF cutoff values and progression to dementia rates. Once subjects in this observation cohort progress to a diagnosis of dementia they will be discontinued from the study.

4.2 Study Population

For entry into the study, the following criteria MUST be met.

4.2.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Subjects (or legally acceptable representative as required by the IRB/IEC) and their study partners have provided a written signed informed consent form/forms (IRB/EC specific) prior to the initiation of any protocol required procedures;

b) For sites participating in intensive PK testing an additional signed written consent by the subjects and their study partners has been obtained prior to the initiation of any intensive PK testing.

2) Target Population

c) Subject meets prodromal Alzheimer's disease criteria as defined by:

i) Memory complaint by subject or study partner that is verified by a study partner.

ii) Abnormal memory function documented by at least 1 of the 4 following criteria:

(1) scoring below the education adjusted cutoff on the Logical Memory II subscale (Delayed Paragraph Recall) from the Wechsler Memory Scale – Revised (the maximum score is 25):

(a) less than or equal to 8 for 16 or more years of education.

(b) less than or equal to 4 for 8 - 15 years of education.

(c) less than or equal to 2 for 0 - 7 years of education. **OR**

(2) Free and Cued Selective Reminding Test (FCSRT) **Total Recall** score of ≤ 39 **OR**

(3) Free and Cued Selective Reminding Test (FCSRT) **Free Recall** score of ≤ 24 **OR**

(4) Free and Cued Selective Reminding Test (FCSRT) **Delayed Free Recall** score of ≤ 8.

d) CSF Aβ42 levels below 200 pg/mL or Total Tau / Aβ42 ratio of ≥ 0.39. Additionally, subjects who meet all other inclusion/exclusion criteria with the exception of the CSF criteria above, may be eligible to be followed in a non-randomized, observational cohort to assess progression rates [see Section 6.4.4.8]);

e) Mini-Mental State Exam score between 24 and 30 (inclusive);

f) Clinical Dementia Rating global score must be = 0.5 at Screening and Baseline **and** the Memory Box score must be at least 0.5 at both Screening and Baseline;

g) Subjects must have an MRI performed during the screening period, prior to randomization, to allow the results to be available at the baseline visit. Results will be centrally read. To be eligible for the study the MRI results must:

i) Be normal (commensurate with age) or demonstrate atrophy consistent with an Alzheimer's disease diagnosis;

ii) Reveal no more than mild to moderate white matter disease;

iii) Up to 2 lacunar infarcts are acceptable however, no lacunes are permitted in the anterior thalamus, genu of internal capsule, or basal forebrain;

iv) Reveal no cortical infarcts;

v) Reveal no more than four microbleeds. N*ote: if an MRI scanner with a field strength > 1.5 T is used, a higher number of microbleeds will be acceptable as determined by the central neuroradiologist*.

vi) vii) Reveal no single area of superficial siderosis (as defined by signal void along the brain pial on GRE studies);

vii) Reveal no focal asymmetric lobar atrophy or other findings suggesting that the primary cause of dementia is better attributed to a cause other than AD;

viii) Reveal no current or prior evidence of macrohemorrhages (> 10 mm);

h) Subject has a score of ≤ 4 on the Modified Hachinski Scale (MHIS) at screening;

i) Subject is not currently being treated with approved marketed medications for AD or if currently being treated is required to be on stable dose for at least 3 months prior to Baseline and the study physician does not anticipate any modifications during the study;

j) Subjects that are not going to be maintained on approved marketed medications for AD should be free of such medications for at least 3 months prior to Baseline with no plans to start such medications during the study;

k) Subjects are determined by the investigator to be medically stable at baseline as determined by medical history, physical examination, laboratory results, and electrocardiogram testing. Patients are physically able and expected to complete the trial as designed;

l) Subjects have a minimum of 6 years of education and were able to read, write and communicate effectively during the premorbid state;

m) Subjects and their study partners have adequate hearing, vision, and language skills to perform neuropsychiatric testing and interviews as specified in the protocol;

n) Subjects are able to ingest oral capsules;

o) Subjects have reliable study partners. A reliable study partner is defined as minimally having approximately 5 hours per week of direct subject contact and being able to fulfill their study specified obligations (including being able to reliably describe and assess changes in the subject's condition) based on the investigator's assessment;

p) Subjects and their study partners must be able to understand and agree to comply with the prescribed dosage regimens and procedures; report for regularly scheduled office visits; and reliably communicate with study personnel about adverse events and concomitant medications;

q) The following treatments will be allowed as long as they were at a stable dose for at least 3 months prior to randomization: donepezil, galantamine, rivastigmine, memantine, vitamin E, fish oil, or estrogen.

3) Age and Sex

r) Women who are postmenopausal and men, ages 45 to 90. Post menopause is defined as:

- Amenorrhea ≥ 12 consecutive months without another cause or
- For women with irregular menstrual periods and on hormone replacement therapy (HRT), a documented serum follicle stimulating hormone (FSH) level > 21.7 mIU/mL

4.2.2 Exclusion Criteria

1) Sex and Reproductive Status

a) WOCBP

For purposes of this study, WOCBP include any female who has experienced menarche and who is not postmenopausal. Post menopause is defined as:

- Amenorrhea ≥ 12 consecutive months without another cause or
- For women with irregular menstrual periods and on hormone replacement therapy (HRT), a documented serum follicle stimulating hormone (FSH) level > 21.7 mIU/mL

Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, skin patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (eg, vasectomy) should be considered to be of childbearing potential.

b) Women who are pregnant or breastfeeding.

c) Women with a positive pregnancy test on enrollment or prior to administration of investigational product.

d) Sexually active fertile men not using effective birth control if their partners are WOCBP.

2) Target Disease Exceptions

a) Subject's diagnosed with Dementia per DSM-IV criteria;

b) Subjects with any other medical condition other than prodromal Alzheimer's disease that could explain the patients memory or cognitive deficits (eg, Vitamin B12 or folate deficiency, abnormal thyroid function, posttraumatic conditions, syphilis, multiple sclerosis or another disorder of neuro-inflammation, Parkinson's disease, vascular or multi-infarct dementia, Huntington's disease, normal pressure hydrocephalus, CNS tumor, progressive supranuclear palsy, seizure disorder (other than childhood febrile seizures), subdural hematoma).

3) Medical History and Concurrent Diseases

a) Subjects with a history of stroke (Note: Subjects with a history of TIA may be enrolled, if occurred at least three months prior to screening and they are prescribed appropriate treatment (eg, platelet aggregation inhibitors);

b) Subjects who are immunocompromised at screening including taking medications that are systemic immunosuppressive treatment such as oral corticosteroids;

c) Subjects with a history of gastrointestinal illnesses including:

i) a current diagnosis of active, peptic ulceration or gastrointestinal bleeding within the last year and/or chronic inflammatory bowel disease, at screening;

ii) a history of any gastrointestinal surgery that could impact upon the absorption of study drug;

iii) a positive Fecal Immunochemical Test (FIT™) during the Screening period (unless subsequent upper and lower GI workup is negative for GI pathology);

iv) chronic or frequent episodes of loose stools;

d) Subjects with a Vitamin B12 or folate deficiency (Note: Subjects with a B12 deficiency may participate in the study if they are on stable Vitamin B12 replacement for at least three months prior to screening and their B12 levels are within normal limits prior to randomization;

e) Subjects with a Geriatric Depression Scale (GDS) score of ≥ 6 at screening;

f) Subjects with any unstable cardiovascular (includes uncontrolled hypertension), pulmonary, gastrointestinal or hepatic disease within 30 days prior to screening;

g) Subjects who have been treated for or have had a diagnosis of schizophrenia or Bipolar Disorder within 3 years, prior to screening;

h) Subjects who have had an active major depressive episode within six months prior to screening;

i) Subjects with a history of neurosyphilis (indicated by a positive RPR test and confirmed by a positive FTA-ABS test);

j) Subjects having a history of drug or alcohol abuse within 12 months prior to screening as defined by DSM-IV-TR criteria;

k) Subjects having a hematologic or solid malignancy diagnoses within 5 years prior to screening (Note: Subjects with a history of localized skin cancer, basal cell or squamous cell carcinoma, may be enrolled in the study as long as they are cancer free prior to randomization. Subjects with other localized cancers (without metastatic spread) who have previously completed their course of treatment more than two years prior to baseline, are not currently receiving treatment and have been in remission may be enrolled only if, in the opinion of the investigator, there is no expectation for recurrence or further cancer treatment during the study period. Antihormonal therapy (ie, tamoxifen) is allowed if the subject's cancer is in remission and the subject is on maintenance therapy to reduce their risk of recurrence;

l) Subjects with active liver disease or a history of hepatic intolerance that in the investigator's judgment, is medically significant;

m) Subjects who have a history or evidence of any medical, neurologic or psychological condition that would expose them to an undue risk of a significant adverse event or interfere with assessments of safety and efficacy during the course of the trial as determined by the clinical judgment of the investigator;

n) Unwilling or unable due to existing medical condition [ie, incompatible pacemaker, some types of aneurysm clips, shrapnel or Implantable Cardioverter-Defibrillator (ICD) device] to have a Magnetic Resonance Image (MRI) at protocol specified time points;

4) Physical and Laboratory Test Findings

a) Subjects having uncontrolled hypertension at screening (eg, repeated diastolic measurements ≥ 96 mmHg);

b) Subjects having a diagnosis of hypothyroidism as indicated by a screening TSH greater than the upper limit of normal and Free T4 Index less than the lower limit of normal

(Note: Subjects with history of hypothyroidism may participate in the study, provided they are euthyroid on stable thyroid replacement therapy for at least 3 months prior to screening);

c) Subjects having either of the following hepatic test abnormalities at screening:
   i) AST or ALT greater than 1.5 times the upper limit of normal;
   ii) Total Bilirubin greater than 2 times the upper limit of normal;

d) Subjects having P-Amylase or Lipase values greater than 2 times upper limit of normal at screening;

e) Subjects at screening having insulin-dependent diabetes mellitus or HbA1C > 7.5%;

f) Subjects at screening having pathologic renal findings as defined by the presence of either of the following criteria:
   i) Calculated GFR < 30 mL/min/1.73m^2 (Cockcroft-Gault formula for GFR estimate);
   ii) Quantitative urine protein/creatinine ratio greater than 0.2. The test maybe repeated. In the event of UTI, the test may be repeated after the UTI has resolved;

g) Subjects having at screening any of the following hematologic abnormalities:
   i) Hemoglobin < 10g/dL;
   ii) WBC < 3.0 x 10^3/mm^3;
   iii) Platelet count < 100,000/mm^3;

h) Subjects at screening who are HIV positive (indicated by a positive confirmatory Western Blot);

i) Subjects at screening having a QTc (Bazett's) and QTc (Fridericia) interval > 450 ms confirmed by repeat measurement or uncontrolled arrhythmia or frequent PVC's (> 5/minute) or Mobitz Type II second or third degree AV block or evidence of acute or subacute myocardial infarction or ischemia. *Note: Subjects with pacemakers and a paced QTc < 475 ms may be enrolled after obtaining a cardiology consult and it is determined by the consulting cardiologist that the subject's cardiac status is stable and does not pose a risk for participation in the trial;*

5) Allergies and Adverse Drug Reactions

a) Subjects having a history of any significant drug allergy (such as Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, anaphylaxis, drug induced hepatotoxicity, etc);

6) Prohibited Treatments and/or Therapies

a) Subjects that have taken an agent with a primary mechanism of action related to Aβ levels or function (eg, γ-secretase inhibitors, Aβ antibodies or vaccines targeting beta-amyloid) within 12 months prior to Baseline;

b) Subjects that required medications for agitation or psychotic features within 3 months prior to Baseline (including all antipsychotic medications);

c) Subjects that have received a new anxiolytic or sleep medication not taken at a stable dose within 30 days prior to Baseline Low dose anxiolytics pre-medications prior to diagnostic testing (eg, neuroimaging, lumbar puncture, etc.) is allowed;

d) Subjects taking illicit drugs or narcotics within 30 days of Baseline or regularly during the study (including morphine, codeine, hydromorphone, oxycodone);

e) Pg-p substrates with narrow therapeutic index, Digoxin;

f) Substrates with metabolism highly dependent on CYP 2C9 and CYP 2C19 and narrow therapeutic index: warfarin, phenytoin, amitriptyline, clomipramine, losartan and proguanil. Diclofenac, ibuprofen, piroxicam and flurboprofen are permitted at low doses (at no more than approximately half the daily recommended dose per label), but prohibited at high chronic doses; For example, ibuprofen concentrations may double when administered with BMS-708163 and therefore, a chronic dose greater than 400 mg would not be advised. Co-administration of BMS-708163 and any substrate with metabolism highly dependent on CYP 2C9 and CYP 2C19 requires close monitoring on an individual patient basis and potential dose reduction;

g) Substrates with metabolism highly dependent on CYP2D6 and narrow therapeutic index including desipramine, nortriptyline, flecainide, propafenon and metoprolol;

h) Substrates with metabolism highly dependent on CYP2C8 and narrow therapeutic index including repaglinide, paclitaxil, and rosiglitazone;

i) Subjects taking the following sedatives or benzodiazepines for anxiety disorders within 30 days screening including chlordiazepoxide, clonazepam, diazepam, flurazepam, meprobamate, triazolam, alprazolam, buspirone, choral hydrate. Subjects may receive a low dose benzodiazepine for sleep as long as it has been at a stable dose for 60 days prior to Baseline;

j) Subjects taking anticholinergic agents within 30 days of Screening including amantadine, atropine, benztropine, cyproheptadine, dicyclomine, diphenhydramine, diphenoxylate, hydroxyzine, hyoscyamine, meclizine, prochlorperazine, trihexyphenidyl, trimethobenzamide;

k) Subjects taking the antiparkinsonian medications within 30 days of screening including bromocriptine, deprenyl, selegiline, levodopa, pergolide, pramipexole;

l) Subjects taking medications with properties to reduce immunologic lymphocytes or immunglobulin levels (eg, rituximab, etanercept and adalimumab) at Screening;

m) Subjects having received any of following medications within 30 days prior to Baseline;

   i) Potent CYP3A4, CYP2C19, and CYP2C9 inhibitors (eg, fluvoxamine, ketoconazole, ticlopidine, amiodarone, fluconazole, isoniazid, amiodarone, chlorpheniramine, cimetadine, clomipramine, methadone, mibefradil, quinidine, ritonavir, indinavir, nelfinavir, clarithromycin, diltiazem, erythromycin, itraconazole, mibefradil, nefazodone and troleandomycin, and verapamil);

n) Subjects receiving tricyclic antidepressants and MAO inhibitors within 30 days of Screening. *(Note: other antidepressants are permitted if the subject has been on a stable dose for 3 months prior to screening and no dose changes are expected throughout the course of the study, refer to Section 5.5.2.2);*

o) Use of grapefruit, grapefruit juice or grapefruit containing products is prohibited 14 days prior to dosing;

7) Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated;

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness;
c) Subjects who reside in a nursing home or skilled nursing facility at Screening;
d) Subjects who were enrolled in any investigational study within 30 days prior to Screening;
e) Subjects unable or unwilling to undergo an MRI at specified time points throughout the study;

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

4.2.3 Discontinuation of Subjects from Treatment

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) (investigational or noninvestigational treatment) for any of the following reasons:

1) Withdrawal of informed consent (subject's decision to withdraw for any reason);
2) Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject;
3) Pregnancy (see Section 7.6.2);
4) Termination of the study by Bristol-Myers Squibb (BMS); **Note: Study has been terminated by sponsor due to evaluation of interim analysis study results** (refer to Amendment 9 for rationale)**.**
5) Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness;
6) Discretion of the investigator;

All subjects who discontinue investigational product should comply with protocol specified follow-up procedures as outlined in Section 6 Study Assessments and Procedures. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study treatment is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (eCRF) page.

4.3 Data Monitoring Committee

The Alzheimer's disease population represents a patient group where BMS has relatively limited patient safety information regarding multiple doses of BMS-708163. As such, an independent Data Monitoring Committee (DMC) will oversee the safety of trial participants.

The DMC review of partially unblinded data will be conducted for safety and clinical outcome measures approximately every 3 months and the DMC will have access to all available data on an unblinded basis at their discretion. BMS will forward all SAEs to the DMC in a timely manner. The DMC may also be consulted for individual patient safety concerns. A DMC charter will further delineate its responsibilities.

Additional interim analyses may be performed in support of Phase 3 protocol design. These analyses might include efficacy in addition to safety data. Additional details of all analyses will be described in the statistical analysis plan.

4.4 Adjudication Committee

An important secondary outcome measure in this protocol is time to progression to dementia (refer to Section 6.4.2.1). Patients with prodromal AD typically progress to mild AD at an estimated rate of 25% per year.[41] Clinical progression will be assessed by the clinician at each site. Sites will apply DSM-IV criteria when determining clinical progression to dementia. To ensure consistent application of the criteria for conversion to dementia, the Adjudication committee will confirm/verify the progression from prodromal AD to dementia based on their review of the subject's data however, the site will be blinded to the Adjudication Committee's assessment. The Adjudication Committee will review specified subject records and appropriate scales. The Committee will also review approximately 10% of cases that have not been determined by the clinician to progress to dementia. Any subject who has progressed to dementia while on study medication will continue to be followed in the treatment phase of this trial. An Adjudication Committee Charter will further delineate its responsibilities. In addition, specific instructions will be provided to the investigative sites regarding their interaction and requirements with the Adjudication Committee.

Subjects who progress to dementia, up to and including the 12 Week Post Treatment/Study Termination Safety Follow-up Visit, will have their data reviewed by the Adjudication Committee for confirmation/verification of progression to dementia.

6 STUDY ASSESSMENTS AND PROCEDURES

6.1 Flow Chart/Time and Events Schedule

Table 6.1-1: Flow Chart for Protocol CN156018

	Pre-treatment: Screening Phase (7 - 75 days)		Treatment Phase (Week 1 - Week 24) End of Week (± 2 days)													
Procedure	**Screen**	**Baseline**	**1[a]**	**2**	**3[a]**	**4**	**5[a]**	**6**	**7[a]**	**8**	**9[a]**	**12**	**16**	**20**	**24**	**Protocol Section**
Eligibility Assessments																
Informed Consent	X															3.3, 4.2.1
Demographic Data	X															6.1.1.1
Entrance Criteria	X	X														4.2.1, 4.2.2
Medical History	X															6.1.1.1
Dementia History	X															4.2, 6.1.1.1
Modified Hachinski Ischemia Scale	X															4.2, 6.1.1.1
Geriatric Depression Scale	X														X	4.2, 6.1.1.1, 6.4.3.5
Physical Examination	X	X													X	6.3.2
Comprehensive Skin Examination and History[b]		X														6.3.4
Screening Safety Laboratory Tests (central laboratory)[c]	X															6.3.5.1
Primary Objective Assessments																
Brief Physical/ Neurological Examination[d]				X		X		X		X		X	X	X		6.3.3

Table 6.1-1: Flow Chart for Protocol CN156018

	Pre-treatment: Screening Phase (7 - 75 days)		Treatment Phase (Week 1 - Week 24) End of Week (± 2 days)													
Procedure	**Screen**	**Baseline**	**1[a]**	**2**	**3[a]**	**4**	**5[a]**	**6**	**7[a]**	**8**	**9[a]**	**12**	**16**	**20**	**24**	**Protocol Section**
Comprehensive Structured Skin Examination[e]						X				X		X			X	5.3.3.3.1
Full Neurological Exam	X	X													X	6.3.3
Vital Signs[f]	X	X		X		X		X		X		X	X	X	X	6.3.5
Physical Measurements[g]		X		X		X		X		X		X	X	X	X	6.3.5
12 Lead ECG (central laboratory)	X	X				X				X		X	X		X	6.3.1
Adverse Events Assessments[h]			X	X	X	X	X	X	X	X	X	X	X	X	X	7.1
Concomitant Medications	X	X		X		X		X		X		X	X	X	X	5.5
Routine Safety Laboratory Tests (central laboratory)[i]		X		X		X				X		X	X		X	6.3.6.2
PT & INR Lab Tests	X													X		6.3.5.1, 6.3.6.2
Thyroid Function Tests	X					X				X		X	X	X	X	6.3.5.1
Fecal immunochemical test (FIT™)[j]	X															6.3.5.1
Secondary Objectives Assessments																
Assessment of Progression to Dementia[k]		X				X						X			X	6.4.2.1
Exploratory Outcome measures																
CDR-SB	X	X										X			X	6.4.3.1

Table 6.1-1: Flow Chart for Protocol CN156018

	Pre-treatment: Screening Phase (7 - 75 days)		Treatment Phase (Week 1 - Week 24) End of Week (± 2 days)													
Procedure	**Screen**	**Baseline**	**1[a]**	**2**	**3[a]**	**4**	**5[a]**	**6**	**7[a]**	**8**	**9[a]**	**12**	**16**	**20**	**24**	**Protocol Section**
MMSE	X														X	6.4.3.1
Neuropsychiatric Inventory Questionnaire (NPI-Q)		X													X	6.4.3.2
ADAS-COG[l]	X	X										X			X	6.4.3.6
Executive Function Tests[m]	X	X										X			X	6.4.3.7
ADCS-ADL/MCI		X										X			X	6.4.3.10
Wechsler Logical Memory Subscale	X															6.4.3.11
Free & Cued Selective Recall Reminding test	X														X	6.4.3.8
Montreal Cognitive Assessment (MoCA)	X														X	6.4.3.4
Sheehan Suicidality Tracking Scale (STS)		X		X		X		X		X		X	X	X	X	6.3.8.1
Columbia Suicide Severity Rating Scale (C-SSRS)				X		X		X		X		X	X	X	X	6.3.8.2
Pharmacokinetic Sampling (trough)[n]				X		X		X		X		X	X	X	X	6.5.1
Pharmacokinetic Sampling (non-trough)[o]						X				X		X			X	6.5.4
Intensive Pharmacokinetic Sampling								X[p]		X[p]		X[p]	X[p]	X[p]		6.5.5, 6.5.5.1

Table 6.1-1: Flow Chart for Protocol CN156018

	Pre-treatment: Screening Phase (7 - 75 days)		Treatment Phase (Week 1 - Week 24) End of Week (± 2 days)													
Procedure	**Screen**	**Baseline**	**1[a]**	**2**	**3[a]**	**4**	**5[a]**	**6**	**7[a]**	**8**	**9[a]**	**12**	**16**	**20**	**24**	**Protocol Section**
CSF Pharmacokinetic Sampling[q]				X											X	6.5.4, 6.5.5
CSF Biomarkers[r]	X			X											X	6.4.3.12
Exploratory Objectives Assessments																
Lymphocytic Phenotyping, Immunoglobulins, Pneumoccoal serotypes		X										X			X	6.4.4.1
TFF3[s]		X										X			X	6.4.4.2
HES1[s]		X										X			X	6.4.4.2
Renal (Cystatin C and Urine Microalbumin)		X										X			X	6.4.4.2
Plasma and mRNA testing		X													X	6.4.4.4
Genetic testing		X														6.4.4.4
Multiplex Biomarker Plasma Sample		X														6.4.4.4
Volumetric and Safety Head MRI[t]		X													X	6.4.4.5
Safety Head MRI[t]								X				X				6.4.4.5
PROCOG (US Only)[u]		X										X			X	6.4.4.7
Clinical Drug Supplies																
Randomization		X														5.2, 6.1.1.2
Dispense Study Drug		X				X				X		X	X	X	X	5.3

[a] Telephone contact only. See Section 6.1.1.4 for information on telephone safety assessments.

[b] A full comprehensive skin exam will be performed at baseline by a dermatologist or dermatologic physician assistant (United States only). At Baseline the dermatology consultant with perform a complete comprehensive skin examination and provide the site with a subject skin diagram documenting the presence of any clinically relevant skin lesions

[c] Laboratory tests include Hematology, Chemistry, Urinalysis with Microscopic Assessment, Drug Screens, and other eligibility assessments. See Section 6.3.6.1 for information on all Screening laboratory assessments.

[d] Brief Physical/Neurological Exam to include oral ulcer evaluation.

[e] Comprehensive structured skin examinations are to be completed by the study physician, continually using the baseline dermatologic assessment and skin diagram. Referral to a dermatologist will be made for any suspicious looking lesions or if there is diagnostic uncertainty regarding skin lesions identified during the structured skin exams. In the event of the emergence of a clinically significant skin lesson a dermatologic consultation and skin biopsy should be obtained.

[f] Vital Signs include sitting and standing orthostatic pulse and blood pressure measurements at every visit with temperature and respirations measured at Screening, Baseline, and end of treatment.

[g] Weight measurements are to be completed at all visits with height measurements completed at the Baseline Visit only.

[h] Adverse Event evaluation includes AEs of Concern (Section 5.3.2).

[i] Laboratory tests include Hematology, Chemistry, Urinalysis with Microscopic Assessment and other routine assessments. See Section 6.3.6.2 for information on all routine laboratory protocol assessments during the study.

[j] Fecal immunochemical test (FIT™) includes subject/study partner home testing kits to assess GI bleeding are to be completed, received, processed and documented at the study center prior to the Baseline Visit. Hemocult Sensa may be substituted for FIT testing at Screening only. Additionally, FIT testing is required for any on-treatment testing of stool for blood.

[k] Includes the diagnostic assessment form, DSMIV criteria and NINCDS-ADRDS criteria. Any time there a worsening of clinical status or a suspicion of progression to dementia during the first 24 weeks of the study, either at a scheduled visit or between scheduled visits, the site needs to complete the procedures listed in the "Unscheduled Visit/Progression Assessment" column of Table 6.1-2. If this is between visits or at a scheduled visit that does not contain cognitive assessments, then all of the procedures listed in the Unscheduled Visit/Progression Assessment" column of Table 6.1-3 are to be completed. This should be conducted in order to determine if the criteria has been reached to support a clinical impression of progression to dementia.

[l] ADAS-cog including: immediate word recall, following commands, constructional praxis, object/finger and naming, ideation praxis, orientation, word recognition, recall of test instructions, comprehension, word finding difficulty, and spoken language difficulty.

[m] Executive Function Test includes: Color Trails (A & B), Category and Letter Fluency and Digit Span (Forwards and Backwards).

[n] Pharmacokinetic trough levels will be collected on all subjects during the dosing period starting at the Week 2 visit.

[o] Non-trough PK samples will be collected at the end of visits on Weeks 4, 8, 12, and 24. PK blood sampling will be collected whenever a subject experiences a serious adverse event (when clinically feasible).

[p] A subset of subjects at specified sites will complete 1 intensive 24-hour PK assessments after 6 weeks on treatment prior to the Week 104 Visit.

[q] A Sample of CSF for PK will be collected at all time points that CSF is collected, after randomization. PK blood sampling will be collected whenever a subject experiences a serious adverse event (when clinically feasible).

[r] An additional PK assessment will be obtained at the time of each lumbar puncture. An ***optional*** peak dosing CSF collection will occur after Week 2 for those subjects agreeing to an additional LP. This additional LP can be performed at any time after week 2 as long as the subject is on a stable dose of study drug for at least 10 days prior to the LP procedure. To achieve the most accurate assessment of the peak pharmacodynamic effect of BMS 708163 on CSF amyloid levels, **all lumbar punctures must be completed 8 - 12 hours post dosing with study drug** (peak CSF concentrations). The lumbar punctures will either be done in the morning following the last dose of study medication taken the evening prior or in the late afternoon following the morning dose. Ideally, the timing of the lumbar punctures will be consistent with the timing of the initial baseline lumbar puncture. If the timing of the subject's daily dosing is changed to conform to the peak CSF LP measurement requirements, the subject must be dosed at the same time each day for a minimum of 10-days prior to the scheduled LP. This will ensure that the LP reflects the peak pharmacodynamic effects of study medication on CSF amyloid prior to the LP procedure.

[s] If notch-related AEs are suspected additional immunophenotyping, TFF3, and HES1 notch biomarkers may be obtained for purposes of clinical correlation.

[t] Patients that are unable (due to existent medical condition, ie, pacemaker or ICD device) or unwilling to have a head MRI completed will be excluded from the study. Screening MRI may be performed at any time between the Screening and Baseline visits. Results from the centrally read MRI must be received by the site ***PRIOR*** to randomization (Baseline) to ensure all inclusion criteria are meet. Refer to Section 6.4.4.5 for more details.

[u] Patient-reported Outcomes in Cognitive Impairment (PROCOG) outcomes measures (for US sites ONLY).

Table 6.1-2: Flow Chart for Protocol CN156018

	Treatment Phase (Week 32 - Week 220[a]) End of Week (± 7 days)																	Safety Follow-up		Un-scheduled (Pro-gression Assess-ment)	
Procedure	32	44	56	68	80	92	104 / DC[b]	116	128	140	152	164	176	188	200	212	220/ DC/ End of Trt[c]	+4	+12	U[d]	Protocol Section
Primary Objective Assessments																					
Physical Exam							X						X				X				6.3.2
Brief Physical/[e] Neurological Examination	X	X	X	X	X	X		X	X	X	X	X		X	X	X					6.3.3
Comprehensive Skin Examination[f]																	X				6.3.4
Comprehensive Structured Skin Examination[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					6.3.4
Full Neurological Exam							X						X				X				6.3.3
Vital Signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		6.3.5
Physical Measurements[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		6.3.5

Table 6.1-2: Flow Chart for Protocol CN156018

	Treatment Phase (Week 32 - Week 220[a]) End of Week (± 7 days)																	Safety Follow-up		Un-scheduled (Pro-gression Assess-ment)	
Procedure	32	44	56	68	80	92	104 / DC[b]	116	128	140	152	164	176	188	200	212	220/ DC/ End of Trt[c]	+4	+12	U[d]	Protocol Section
12 Lead ECG (central laboratory)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				6.3.1
Adverse Events Assessments[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		7.1
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		5.5
Routine Safety Laboratory Tests[k] (central laboratory)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		6.3.6.2
PT & INR Laboratory testing						X															6.3.6.2, 6.3.6.2
Thyroid Function Tests	X		X		X		X		X		X		X		X		X				6.3.6.1

Table 6.1-2: Flow Chart for Protocol CN156018

	Treatment Phase (Week 32 - Week 220[a]) End of Week (± 7 days)																	Safety Follow-up		Un-scheduled (Pro-gression Assess-ment)	
Procedure	32	44	56	68	80	92	104 / DC[b]	116	128	140	152	164	176	188	200	212	220/ DC/ End of Trt[c]	+4	+12	U[d]	Protocol Section
Secondary Objectives Assessments																					
Assessment of Progression to Dementia	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	6.4.2.1
Exploratory Outcome measures																					
CDR-SB	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	6.4.3.1
MMSE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	6.4.3.2
Geriatric Depression Scale	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	6.4.3.5
Neuropsychiatric Inventory Questionnaire (NPI-Q)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	6.4.3.3
ADAS-COG[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	6.4.3.6

Table 6.1-2: Flow Chart for Protocol CN156018

	Treatment Phase (Week 32 - Week 220[a]) End of Week (± 7 days)																	Safety Follow-up		Un-scheduled (Pro-gression Assess-ment)	
Procedure	32	44	56	68	80	92	104 / DC[b]	116	128	140	152	164	176	188	200	212	220/ DC/ End of Trt[c]	+4	+12	U[d]	Protocol Section
Executive Function Tests[m]	X		X		X		X		X		X		X				X			X	6.4.3.7
ADCS-MCI-ADL	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	6.4.3.10
Free & Cued Selective Recall Reminding test	X		X		X		X		X		X		X				X			X	6.4.3.8
Montreal Cognitive Assessment (MoCA)			X				X						X				X			X	6.4.3.4
Sheehan Suicidality Tracking Scale (STS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	6.3.8.1
Columbia-Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	6.3.8.2
Pharmacokinetic Sampling (trough)[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				6.5.1

Table 6.1-2: Flow Chart for Protocol CN156018

	Treatment Phase (Week 32 - Week 220[a]) End of Week (± 7 days)																	Safety Follow-up		Un-scheduled (Pro-gression Assess-ment)	
Procedure	32	44	56	68	80	92	104 / DC[b]	116	128	140	152	164	176	188	200	212	220/ DC/ End of Trt[c]	+4	+12	U[d]	Protocol Section
Pharmacokinetic Sampling(non-trough)[o]	X		X		X		X		X		X		X				X				6.5.4
Intensive PK	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]														6.5.5
CSF Pharmacokinetic Sampling							X														6.5.4, 6.5.5
CSF Biomarkers[q]							X														6.4.4.3, 6.4.3.12
Exploratory Objectives Assessments																					
Lymphocytic Phenotyping, Immunoglobulins, Pneumoccoal serotypes	X		X		X		X		X		X		X				X				6.4.4.1
TFF3[r]	X		X		X		X		X		X		X				X				6.4.4.2

Table 6.1-2: Flow Chart for Protocol CN156018

	Treatment Phase (Week 32 - Week 220[a]) End of Week (± 7 days)																	Safety Follow-up		Un-scheduled (Pro-gression Assess-ment)	
Procedure	32	44	56	68	80	92	104 / DC[b]	116	128	140	152	164	176	188	200	212	220/ DC/ End of Trt[c]	+4	+12	U[d]	Protocol Section
Renal (Cystatin C and Urine Microalbumin)	X		X		X		X		X		X		X				X				6.4.4.2
Plasma and mRNA testing							X														6.4.4.4
Multiplex Biomarker Plasma Sample							X														6.4.4.4
Safety and Volumetric Head MRI			X				X				X										6.4.4.5
Safety Head MRI	X	X		X	X	X		X	X	X		X	X	X	X	X	X				6.4.4.5
PROCOG[s]							X						X				X				6.4.4.7
Clinical Drug Supplies																					
Dispense Study Drug	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					5.3

[a] Subjects continuing on treatment beyond the End of Week 104 Visit (until the overall last patient last treatment visit) will continue to have visits approximately every 12 weeks until approximately September 2013. All procedures scheduled for End of Week 220/DC/End of treatment should be performed at the time of actual discontinuation/end of treatment.

[b] End of treatment procedures to be completed if subject discontinues at or prior to Week 104 of the Treatment Phase.

[c] Week 220/DC/End of treatment procedures to be completed upon subject discontinuation anytime after Week 104

[d] Any time there a worsening of clinical status or a suspicion of progression to dementia during weeks 32 - 220 of the study, either at a scheduled visit or between scheduled visits, the site needs to complete the procedures listed in the "Unscheduled Visit/Progression Assessment" column of Table 6.1-2. If this is between visits or at a scheduled visit that does not contain cognitive assessments, then all of the procedures listed in the Unscheduled Visit/Progression Assessment" column of Table 6.1-2 are to be completed. This should be conducted in order to determine if the criteria has been reached to support a clinical impression of progression to dementia.

[e] Brief Physical/Neurological Exam to include oral ulcer evaluation.

[f] A comprehensive skin examination will be performed at the end of study by a dermatologist or dermatologic physician assistant (United States Only).

[g] Comprehensive structured skin examinations are to be completed by the study physician, continually using the baseline dermatologic assessment and skin diagram. Referral to a dermatologist will be made for any suspicious looking lesions or if there is diagnostic uncertainty regarding skin lesions identified during the structured skin exams. In the event of the emergence of a clinically significant skin lesson a dermatologic consultation and skin biopsy should be obtained.

[h] Vital Signs include sitting and standing orthostatic pulse and blood pressure measurements at every visit with temperature and respirations measured at Screening, Baseline, and end of treatment.

[i] Weight measurements are to be completed at all visits with height measurements completed at the Baseline Visit only.

[j] Adverse Event evaluation includes AEs of Concern (Section 5.3.2).

[k] Laboratory tests include Hematology, Chemistry, Urinalysis with Microscopic Assessment and other routine assessments. Exploratory renal laboratory tests will also be done at visits specified in section 6.3.6.2. Also See Section 6.3.6.2 for information on all routine laboratory protocol assessments during the Treatment Phase.

[l] ADAS-cog including: immediate word recall, following commands, constructional praxis, object/finger and naming, ideation praxis, orientation, word recognition, recall of test instructions, comprehension, word finding difficulty, and spoken language difficulty.

[m] Executive Function Test includes: Color Trails (A & B), Category and Letter Fluency and Digit Span (Forwards and Backwards).

[n] Pharmacokinetic trough levels will be collected at all visits & non trough levels will be collected every 6 months.

[o] A subset of subjects at specified sites will complete 1 intensive 24-hour PK assessments after 6 weeks on treatment prior to the Week 104 Visit.

[p] A Sample of CSF for PK will be collected at all time points that CSF is collected, after randomization.

[q] To achieve the most accurate assessment of the peak pharmacodynamic effect of BMS-708163 on CSF amyloid levels, **at the Week 104 lumbar puncture must be completed 8-12 hours post dosing with study drug (peak CSF concentrations).**The lumbar puncture should be performed at approximately the

same time of day as the baseline procedure. If the timing of the subject's daily dosing is changed to conform to the peak CSF LP measurement requirements, the subject must be dosed at the same time each day for a minimum of 10-days prior to the scheduled LP. This will ensure that the LP reflects the peak pharmacodynamic effects of study medication on CSF amyloid prior to the LP procedure.

[r] If notch-related AEs are suspected additional immunophenotyping, TFF3 may be obtained for purposes of clinical correlation.

[s] Patient-reported Outcomes in Cognitive Impairment (PROCOG) outcomes measures (for US sites ONLY).

Table 6.1-3: Flow Chart for Protocol CN156018 - Observational Cohort			
	Observational Cohort Assessments		
Procedure	**Baseline[a]**	**Every 12 Weeks (± 7 days)**	**Protocol Section**
Assessments			
Assessment of Progression to Dementia	X	X	6.4.2.1
CDR-SB	X	X	6.4.2.2
MMSE		X	6.4.3.1
Neuropsychiatric Inventoy Questionnaire (NPI-Q)	X	X	6.4.3.2
ADAS-COG (ADNI Modified)	X	X	6.4.3.6
Executive Function Tests	X	X	6.4.3.7
ADCS-MCI-ADL	X	X	6.4.3.10
Free & Cued Selective Recall Reminding test		X	6.4.3.8
Montreal Cognitive Assessment (MoCA)		X	6.4.3.3
Sheehan Suicidality Tracking Scale (STS)	X	X	6.3.8.1
Columbia-Suicide Severity Rating Scale (C-SSRS)		X	6.3.8.2
Safety and Volumetric Head MRI	X	X[b]	6.4.4.5
Concomitant Medication Tracking[c]	X	X	5.5

[a] All Screening assessments must be completed and the subject must meet all inclusion/exclusion criteria (with the exception of the Aβ42 level of < 200 pg/mL or a Total Tau/Aβ42 ratio of ≥ 0.39) to be eligible for the Observational Cohort. Refer to Section 6.4.4.8 for additional details.

[b] On-study MRI should be done at the week 60 visit, or the next scheduled visit for subjects who have surpassed week 60.

[c] Only CNS acting medications are required to be captured for Observational Cohort participants.

Table 6.1-4: Flow Chart for Protocol CN156018 - Long-Term Follow-up and Post Treatment/Study Termination Safety Follow-Up Visits

Procedure	LTFU Every 12 Weeks (+ 7 days)	4 Week Post Txt	12 Week Post Txt	24 Week Post Txt[a]	Protocol Section
Assessments					
Assessment of Progression to Dementia	X		X		6.4.2.1
CDR-SB	X		X		6.4.2.2
MMSE	X		X		6.4.3.1
ADAS-COG	X		X		6.4.3.6
Geriatric Depression Scale	X		X		6.4.3.5
DSM-IV-TR	X		X		6.4.2.1
NINCDS-ADRDA	X		X		6.4.2.1
ADCS-MCI-ADL	X		X		6.4.3.10
Vital Signs[b]	X	X	X		6.3.5
Physical Measurements[c]	X	X	X		6.3.5
Routine Safety Laboratory Tests, including exploratory renal laboratory tests (central laboratory)	X	X	X		6.3.6.2
Renal (Cystatin C and Urine Microalbumin)			X		6.4.4.2
Comprehensive Structured Skin Examination			X		6.3.4
Comprehensive Skin Examination				X	6.3.4
12 Lead ECG (central laboratory)	X				6.3.1
Adverse Event Assessments	X	X	X		7.1
Concomitant Medication Tracking[d]	X	X	X		5.5

[a] Post Treatment/Study Termination Safety Follow-up Visit at 24 Weeks will only include a comprehensive skin examination by a dermatologist (or dermatologic physician's assistant in the United States).

[b] Vital Signs include sitting and standing orthostatic pulse and blood pressure measurements.

[c] Weight measurements are to be completed during Long-term Follow-up.

[d] Only CNS acting medications are required to be captured for Long-term Follow-up participants.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The primary endpoint of this study is safety and tolerability. The sample size of 135 subjects per group is chosen empirically rather than based on the statistical power consideration. However, it should be noted that with 135 subjects per dose group, the probability of observing at least one specific AE is satisfactorily high at each dose group if the true event rate of that AE is within the commonly observed ranges, as shown in Table 8.1-1 with a list of assumed true event rates. For example, the probability of observing at least 1 specific AE is 98% at each dose group if the true event rate of that AE is 3% (Table 8.1-1). Table 8.1-2 shows the probability of observing at least one event difference assuming different event rates for each treatment group. In addition, the 95% exact confidence interval of 10% (13 events out of 135 subjects) event rate in each group is (0.05, 0.16).

Table 8.1-1: Probability of Observing a Given Adverse Event

Assumed AE incidence rate	Probability of observing at least 1 AE out of 135 patients[a]
0.1%	12.6%
0.5%	49.1%
1%	74.2%
2%	93.5%
3%	98.4%

[a] Assumes a distribution of Binomial (n = 135, probability of event given in the first column).

Table 8.1-2: Probability of Observing at Least One Incidence Difference

		AE incidence rate (%) for Active				
AE incidence rate (%) for Placebo	0.1	0.5	1	2	3	
0.1	22.3%					
0.5	51.4%	60.9%				
1	73.2%	71.8%	74.1%			
2	92.0%	87.0%	83.2%	82.2%		
3	97.6%	95.0%	90.9%	86.1%	85.6%	

8.2 Populations for Analyses

- The **Enrolled Sample** comprises all subjects who sign informed consent and obtain an enrollment number

- The **Randomized Sample** comprises all subjects who are randomized in the double-blind treatment phase.
- The **Safety Sample** comprises all subjects in the Randomized Sample who take at least one dose of double-blind study medication as indicated on the study therapy form.

All safety analyses will be performed on the Safety Sample, except for listings of deaths and serious adverse events (SAEs), which will use the Enrolled Sample. For safety analyses, if a subject receives a treatment other than one to which he or she was randomized, this subject will be analyzed as treated (based on the first medication kit number received after randomization).

All efficacy analyses will be performed on the Randomized Sample, unless otherwise specified. All efficacy analyses will be performed at Baseline (if evaluated at baseline), at endpoint (104 week treatment period), and at each specified study month. Efficacy analyses will be performed using observed cases. For efficacy analyses, if a subject receives a treatment other than the one to which he or she was randomized, this subject will be analyzed as randomized.

8.3 Endpoint Definitions

Safety endpoints: Adverse Events, Physical and Neurological Examinations, Vital Signs, Laboratory Assessments, ECGs, and Safety Head MRI findings.

Clinical endpoints: CDR-SB, ADAS-cog, NPI, ADCS-MCI-ADL and rate of progression from prodromal AD to mild/moderate AD.

Biomarker endpoints: CSF biomarkers (Aβ-40 and Aβ-42, total Tau, total Tau/Aβ42 ratio and phosphorylated Tau) and volumetric brain magnetic resonance imaging measurements, and PET

Pharmacokinetic Measures: Pharmacokinetic trough plasma concentrations of BMS-708163 (and metabolites if warranted) will be determined in all subjects at all visits during the treatment phase starting at the Week 2 visit. A subset of subjects will complete intensive 24-hour PK sampling (after 6 weeks on treatment and prior to the Week 104 visit). Free BMS-708163 may be determined in each subject at the highest expected concentration using ex vivo plasma protein binding techniques, if warranted.

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Baseline demographic characteristics (age, gender, race, ethnicity, weight) and other important baseline biomarkers and clinical measures (Aβ42, ADAS-cog, etc) will be summarized by randomized treatment group and overall for the Randomized Sample. The mean, median, range and standard deviation will be used to describe continuous variables. Frequency distributions will be tabulated for categorical variables.

8.4.2 Safety Analyses

Safety and tolerability will be evaluated by reports of adverse events (AEs) and clinically significant changes in ECGs, Safety Head MRI findings, vital signs, physical examination

findings and laboratory tests. The incidence of adverse events will be tabulated by treatment, according to severity, and drug-relationship. All safety analyses will be performed on the safety sample; subjects will be analyzed as treated. Special safety lab results, such as notch lymphocyte, GI and renal safety test, will be included in laboratory analyses. Safety analyses will be performed separately for the double-blind phase and for the safety follow-up phase. The safety data presentation for the follow-up phase will be by the original assigned treatment.

8.4.3 Efficacy Analyses

Confidence intervals will be reported at the 95% level, if not otherwise specified.

In order to assess the predictive value of baseline CSF biomarkers (Aβ40, and Aβ42, total Tau, total Tau/Aβ42 ratio, and phosphorylated Tau) on progression to dementia, the relationship between each of CSF biomarker and time to progression to dementia will be assessed by separate stratified Cox proportional hazards model on the Randomized Sample. The Cox model will include treatment, age, gender, education and individual baseline biomarker as covariates and ApoE4 status and baseline status of acetylcholinesterase inhibitor treatment as stratified variables. The parameter estimate and 95% CI for the hazard ratio for one unit increase in the biomarker will be reported. Patients who do not have progression to AD will be censored on their last visit date.

In order to validate Aβ42 screening cutoff point of 200 pg/mL, stratified logistic analysis will be carried out on the combined dataset of placebo group and observational cohort. The logistic model will have progression to AD (yes/no) as a binary dependent variable and age, gender, education and Aβ42 screening value as covariates and ApoE4 status and baseline status of acetylcholinesterase inhibitor treatment as stratified variables.

Time to progression to dementia will be obtained from Kaplan-Meier maximum likelihood estimates for each treatment group on the Randomized Sample.

For each of the continuous efficacy outcome measurements (CDR-SB and ADAS-Cog, etc), the change from baseline to post-baseline scores (up to 24 months) over time from the Randomized Sample will be analyzed using a linear mixed effects model repeated measures (MMRM) with maximum likelihood estimation. The model will include treatment, time, baseline primary efficacy score, the interaction between baseline primary efficacy score and time, baseline MRI volume, APOE status, baseline status of acetylcholinesterase inhibitor treatment and the interaction between treatment and time as covariates. Time is classified into months (3, 6, 9, 12, 15, 18, 21, and 24) and treated as a categorical variable. An unstructured covariance matrix will be used to represent the correlation of the repeated measures within each subject. Model based adjusted mean change score from baseline (LS means) at each study month and 95% CI for the treatment difference will be reported.

Pearson's correlation coefficient will be used to estimate the linear relationship between clinical outcomes such as CDR-SB with biomarkers at study months when both measurements are available. Post-treatment follow-up data from the safety follow-up phase will be considered in sensitivity analyses. Trending of clinical rating scales during the active treatment period differing

from those after discontinuation from treatment will be investigated. Number of progressions after study medication discontinuation will also be tabulated, but will not be adjudicated.

8.4.4 Pharmacokinetic Analyses

The BMS-708163 plasma concentrations obtained by sparse and intensive sampling of individual subjects will be used to build a population PK model to estimate PK parameters (eg, CL/F, Vd/F, and ka). Summary statistics will be provided for all drug concentration data and for PK parameters following intensive PK sampling. Possible covariate effects on PK parameters (eg, gender effect on CL/F) may be identified and quantified. The influence of symptomatic co-medication (ChEI) on PK parameters may also be explored. Using model-based estimations, the PK parameters will be used to compute individual exposure measures (eg, AUC, Cmax, Cmin). The PK data derived from this study may also be pooled with data from other studies to refine the model-based analysis to optimize dose selection for Phase 3. This population analysis will be presented separately.

For subjects having intensive pharmacokinetic sampling, individual subject pharmacokinetic parameter values (eg, Cmax, Tmax, Cmin, AUC_{TAU}) will be derived by non-compartmental methods by a validated pharmacokinetic analysis program.

The CSF samples taken during the study will also be assayed for BMS-708163.

8.4.5 Pharmacodynamic Analyses

The corrolation between BMS-708163 exposure and CSF concentrations of Aβ40, Aβ42, tau, and phosphorylated tau, and/or their reductions from baseline will be explored. Relationships between BMS-708163 exposure measures and efficacy scores (eg, ADAS-cog changes from baseline) will be explored. Similar exploratory analyses may be performed for other cognitive and/or safety endpoints. If warranted, CSF biomarker response and safety/efficacy (ie, cognition) events and their relation to free drug concentrations may be explored as well based on the fraction bound to plasma proteins.

8.4.6 Pharmacogenomic Analyses

Details of the pharmacogenomics analyses are noted in Amendment 01.

APOE:

Part of the efficacy analysis will make use of an analysis of covariance (ANCOVA) model, controlling for the APOE4 genotype (positive vs negative). This takes into account published clinical Phase 2 study findings with rosiglitazone indicating APOE genotype related treatment differences[56] as well as clinical Phase 2 indicating genotype related treatment differences with the humanized Aβ antibody Bapineuzumab.[57]

CYP Enzyme Genotyping:

Metabolism of BMS-708163 is primarily mediated via CYP3A4, CYP2C9, and CYP2C19, while the involvement of additional CYP enzymes is possible. In order to better understand PK

variability, relations between polymorphisms of CYP enzymes, in particular CYP2C9 and 2C19, and exposures will be explored.

8.4.7 Outcomes Research Analyses

The mean change from baseline to each scheduled visit in PROCOG will be analyzed similarly to that for efficacy endpoint.

8.4.8 Other Analyses

8.4.8.1 Biomarker Analyses

The mean change from baseline to each scheduled visit in the proposed biomarker measures (CSF biomarkers, plasma biomarkers and Volumetric MRI) will be analyzed based on Safety Sample. The analysis will make use of ANCOVA model, controlling for key covariates (APOE4 genotype, and concurrent AD medication use) and adjusting for corresponding baseline.

Specifically, for plasma TFF3 or CSF and plasma Aβ40 and Aβ42, the ANCOVA model will be applied to the log-transformed percentage of baseline measures. If multiple post-treatment time points were measured, a linear mixed effect model with fixed dose effect and time effect (repeated measures) will be used for the analysis.

For whole blood mRNA genes (HES-1), the gene expression level will be normalized to an internal housekeeping gene (eg, GAPDH) before applying statistical analysis. The change from baseline of the normalized gene expression levels will be fitted into the ANCOVA model.

8.5 Interim Analyses

Interim analysis may be performed on safety and efficacy parameters, CSF biomarkers, and clinical PK and PD data to help inform the development of Phase 3 protocols. The results of these analyses will be presented to a limited number of BMS employees in an unblinded manner. Investigators and subjects will remain blinded. No adjustment to significance levels for the final analyses will be made due to this interim analysis because none of the efficacy endpoints is primary and the sample size determination is not based on efficacy.

Additional details of the interim analysis will be described in the statistical analysis plan.

9 ADMINISTRATIVE SECTION

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects. Any significant deviation must be documented in the CRF.