Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Undecided		
Name of Active Ingredient: BMS-708163		

SYNOPSIS

Final Clinical Study Report for Study CN156013

TITLE OF STUDY: 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 Mild to Moderate Alzheimer's Disease

INVESTIGATORS/STUDY CENTERS: 41 sites in 4 countries enrolled at least 1 patient.

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 26-Feb-2009 **CLINICAL PHASE:** Phase 2

Study Completion Date: 07-Jun-2010

OBJECTIVES:

Primary Objective: To assess the safety and tolerability of BMS-708163 in patients with mild to moderate Alzheimer's disease (AD)

Secondary Objectives: To characterize pharmacodynamic (PD) effects of BMS-708163 on:

- Cerebral Spinal Fluid (CSF) biomarkers of mechanism of action (Aβ40, Aβ42) and putative biomarkers of neurodegeneration in AD (total Tau, phosphorylated Tau) in a subset of patients.
- Cognition as assessed with the 11-item Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-cog), ADAS-cog memory score, executive function score (Color Trails Making Tests, Category and Letter Fluency Tests, Digit Span - forwards and backwards), a derived Global Cognition score (summary z-score), and the Mini Mental State Exam (MMSE).
- Function in daily living as assessed with the Alzheimer's Disease Cooperative Study - Activities of Daily Living Scale (ADCS-ADL).
- Global clinical impression as assessed with the Clinical Dementia Rating-Sum of Boxes (CDR-SB).

METHODOLOGY: The study is a multicenter, randomized, double-blind, 5-arm, fixed-dose, placebo-controlled, 24-week, parallel-group study, followed by a 12-week washout period. Patients were randomly assigned in a double-blind manner to 1 of the following treatment groups: placebo; 25 mg, 50 mg, 100 mg, or 125 mg BMS-708163 once daily. Treatment allocation was balanced by mild versus moderate dementia

(MMSE 16-20/21-26); AD co-medications (ChEI and/or memantine: yes/no); consent for spinal taps (yes/no), and consent for intensive pharmacokinetic (PK) assessments.

During the first 12 weeks after randomization, patient safety visits occurred every 2 weeks with telephone assessments occurring on alternating weeks. Clinical outcomes (cognitive tests, CDR-SB, and ADCS-ADL) were performed at baseline, Week 12, the end of treatment, and during the washout phase. MRIs and lumbar punctures were performed in a subset of patients at baseline/screening, Week 12 (CSF only), and end of treatment. All patients had trough PK assessments starting at the Week 2 visit, at all subsequent visits during the treatment period, and at the first visit in the 12-week washout phase for those patients who participated in the washout phase. Additional non-trough PK assessments were completed at the time CSF samples were obtained and at the end of visits at Weeks 4, 8, 12, 18, and 24. A subset of patients completed intensive 24-hour PK assessments at some point after 6 weeks on study treatment and prior to the Week 12 visit.

The washout phase was discontinued once Amendment 05 was approved, and patients in the washout phase were scheduled for an end of study visit. Adverse Events (AEs) were collected for up to 30 days after completing the study and until resolution for Serious Adverse Events (SAEs).

NUMBER OF SUBJECTS (Planned and Analyzed): A total of 338 patients were enrolled into the study, of which 209 patients were randomized into the double-blind phase (41 patients in the 50-mg group and 42 patients in each of the other groups). Since the primary objective of this study was to characterize the safety and tolerability of BMS-708163, a target sample size of 40 patients per arm was chosen empirically rather than based on statistical power consideration.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: The study population included male and female outpatients between the ages of 50 and 90, with a National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association and a Diagnostic and Statistical Manual, Fourth Edition, Text Revision diagnosis of probable AD of mild to moderate severity (MMSE 16 to 26). Patients being treated with approved medications for AD were required to have had stable treatment for at least 2 months prior to screening. Patients not receiving approved marketed medications for AD at study entry were to remain free of such medications during the study.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Investigational product was BMS-708163 25 mg capsules and matching placebo capsules. The double-blind dosing period was 24 weeks. Batch numbers were 8H34320, 9A47176, 9C55053, and 9F54414.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Reference therapy was matching placebo capsules for BMS-708163 25 mg. The double-blind dosing period was 24 weeks. Batch numbers were 8H31547, 8L43931, 9D48992, and 9F51062.

CRITERIA FOR EVALUATION:

Safety and Tolerability: The safety and tolerability of BMS-708163 were evaluated using reports of AEs and clinically significant changes in laboratory tests, electrocardiograms (ECGs), vital signs, physical examination findings, and brain magnetic resonance imaging (MRI).

Cognitive and Functional Outcomes: Assessments were based on the characterization of PD effects of BMS-708163 on (i) CSF biomarkers of mechanism of action (Aβ40, Aβ42) and putative biomarkers of neurodegeneration in AD (total Tau, phosphorylated Tau); (ii) cognition as assessed with the ADAS-cog, ADAS-cog memory score, executive function score, a derived Global Cognition score (summary z-score), MMSE; (iii) function in daily living as assessed with the ADCS-ADL; and (iv) global clinical impression as assessed with the CDR-SB.

STATISTICAL CONSIDERATIONS: Adverse events were classified by Primary System Organ Class (SOC) and Preferred Term according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 13.0. The incidence rates of AEs were tabulated by treatment group. Incidence tables of AEs related to study drug (those AEs considered by investigators as related to study treatment), AEs leading to discontinuation of study treatment, and SAEs were summarized. In addition, the incidence of AEs was summarized by treatment group and by time category according to study day of first onset. The incidence rates of AEs were also summarized for subgroups defined by their concurrent use of cholinesterase inhibitors, concurrent use of approved AD medications, and those who had potentially significant urine glucose measurements. Treatment-emergent AEs were defined as those with an onset date on or after the first day of double-blind dosing.

The incidence of potentially clinically relevant changes in laboratory values was tabulated for the double-blind phase by treatment group. The change from baseline at all post-baseline visits, including the double-blind phase and washout phase, was summarized by descriptive statistics. The incidence of potentially clinically relevant changes or events in laboratory values was tabulated by status at baseline (i.e., normal vs abnormal) for the double-blind phase. The incidence of potentially clinically relevant changes in vital signs was tabulated for the double-blind and washout phases, and presented by treatment group. Changes in body weight over the scheduled visits were summarized by descriptive statistics. The percentage of patients showing clinically relevant weight gain (≥ 7% increase from baseline) and clinically relevant weight loss (≥ 7% decrease from baseline in body weight) was summarized.

Potentially clinically relevant changes in ECGs were tabulated for the double-blind phase and presented by treatment group. Change from baseline of quantitative parameters (e.g., QT, QTc, heat rate, etc.) was summarized using descriptive statistics based on data from the Safety Sample.

For each cognition assessment (i.e., ADAS-cog, ADAS-cog memory score, executive function score, global cognition score, MMSE), the change from baseline to post-baseline scores over time from the OC dataset of the Randomized Sample was analyzed using a mixed-effects model repeated measures (MMRM) with a restricted maximum likelihood estimation. The model included the treatment, time, treatment-by-time interaction, and baseline-by-time interaction as main effects and included the corresponding baseline score and key baseline factors (i.e., MMSE score, apolipoprotein E4 status, and baseline status of concomitant AD medication use) as covariates. Time was measured in weeks (12 and 24) and was treated as a categorical variable in the model. An unstructured covariance matrix was used to represent the correlation of the repeated measures within-patient errors. At Weeks 12 and 24, the model-based adjusted mean change score from baseline and the 95% confidence interval (CI) for the treatment difference between active doses and placebo were presented.

The change from baseline to post-baseline scores in ADCS-ADL and CDR-SB from the observed case (OC) dataset were analyzed similarly to that for ADAS-cog.

For CSF biomarkers, the geometric mean over baseline of Aβ38, Aβ40, and Aβ42 at Weeks 12 and 24 was analyzed. The mean change from baseline of total Tau and phosphorylated Tau at Weeks 12 and 24 was also analyzed.

For all statistical analyses, no adjustments were made for multiple comparisons. Nominal P-values were provided for descriptive purposes and should be interpreted with caution.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics: A total of 338 patients were enrolled into the study, of which 209 patients were randomized into the double-blind phase (Table 1). The rates of discontinuation for any reason during the double-blind phase ranged from 21.4% in the 25-mg group to 50.0% in the 125-mg group, vs 19.0% for placebo. The most common reason for study discontinuation was

AE, which ranged from 10% to 12% in the 25-mg and 50-mg dose groups to about a third of patients in the 100-mg and 125-mg dose groups (vs 10% for placebo).

Across groups, the median age was 75 years, and nearly all patients were white (96.2%) (Table 2). The mean time since initial Alzheimer's diagnosis was almost 1.5 times higher in the 125-mg group (41 months) compared to placebo (26 months) and the other treatment groups (ranging from 27 to 32 months). While approximately 40% of patients in the placebo and 100-mg groups were male, rates in the other groups were approximately 60%. Rates of APOE4 positive genotype ranged across the treatment groups from 52% to 73%, with a rate of 57% in the placebo group.

Baseline measures of function in daily living, global clinical impression, and cognition were generally consistent between groups.

Table 1: Disposition of Patients for Double-blind Phase, Enrolled Sample

Patient Status	Number of Patients (%)					
	Placebo	25 mg	50 mg	100 mg	125 mg	Total
Enrolled	n/a	n/a	n/a	n/a	n/a	338
Not Randomized	n/a	n/a	n/a	n/a	n/a	129
Randomized into Double-blind Phase	42	42	41	42	42	209
Discontinued from Double-blind Phase [a]	8 (19.0)	9 (21.4)	10 (24.4)	18 (42.9)	21 (50.0)	66 (31.6)
Lack of efficacy	2 (4.8)	0	0	0	1 (2.4)	3 (1.4)
Adverse event	4 (9.5)	4 (9.5)	5 (12.2)	15 (35.7)	14 (33.3)	42 (20.1)
Patient withdrew consent	1 (2.4)	4 (9.5)	3 (7.3)	2 (4.8)	3 (7.1)	13 (6.2)
Death	0	0	0	0	0	0
Lost to follow-up	0	0	0	0	1 (2.4)	1 (0.5)
Poor / non-compliance	0	1 (2.4)	1 (2.4)	0	1 (2.4)	3 (1.4)
Pregnancy	0	0	0	0	0	0
Subject no longer meets study criteria	0	0	1 (2.4)	0	0	1 (0.5)
Administrative reason by sponsor	0	0	0	0	0	0
Other	1 (2.4)	0	0	1 (2.4)	1 (2.4)	3 (1.4)
Completed Double-blind Phase [a]	34 (81.0)	33 (78.6)	31 (75.6)	24 (57.1)	21 (50.0)	143 (68.4)

[a] Percentages are based on the number of patients who were randomized.

Table 2: Demographics and Baseline Characteristics, Randomized Sample

	Statistic [a]	Placebo (N=42)	25 mg (N=42)	50 mg (N=41)	100 mg (N=42)	125 mg (N=42)	Total (N=209)
Age (years)							
	n	42	42	41	42	42	209
	Mean (SD)	73.7 (10.56)	73.6 (8.21)	74.3 (8.76)	72.9 (8.13)	74.0 (8.14)	73.7 (8.74)
	Median	76.0	73.0	76.0	74.0	74.5	75.0
	Min-Max	50-90	51-87	55-89	52-89	54-89	50-90
Age Category							
<65	n (%)	10 (23.8)	5 (11.9)	6 (14.6)	7 (16.7)	5 (11.9)	33 (15.8)
65-86	n (%)	29 (69.0)	36 (85.7)	34 (82.9)	34 (81.0)	34 (81.0)	167 (79.9)
>86	n (%)	3 (7.1)	1 (2.4)	1 (2.4)	1 (2.4)	3 (7.1)	9 (4.3)
Gender							
Male	n (%)	17 (40.5)	26 (61.9)	23 (56.1)	18 (42.9)	25 (59.5)	109 (52.2)
Female	n (%)	25 (59.5)	16 (38.1)	18 (43.9)	24 (57.1)	17 (40.5)	100 (47.8)
Race							
White	n (%)	41 (97.6)	40 (95.2)	40 (97.6)	40 (95.2)	40 (95.2)	201 (96.2)
Black/African American	n (%)	1 (2.4)	1 (2.4)	0	0	1 (2.4)	3 (1.4)
Asian	n (%)	0	1 (2.4)	1 (2.4)	1 (2.4)	0	3 (1.4)
American Indian/Alaska Native	n (%)	0	0	0	1 (2.4)	0	1 (0.5)
Other	n (%)	0	0	0	0	1 (2.4)	1 (0.5)
Time (months) Since Initial AD Diagnosis							
	n	39	37	38	40	41	195
	Mean (SD)	25.8 (24.49)	26.9 (26.65)	31.5 (26.13)	25.8 (21.77)	41.1 (31.85)	30.3 (26.82)
	Median	18.9	17.2	24.8	23.2	35.5	23.6
	Min-Max	-1-112	0-106	0-112	1-95	4-136	-1-136
	Missing	3	5	3	2	1	14

[a] Percentages are based on the number of randomized patients. AD Diagnosis dates have been imputed if partially missing. If only the month and year are available, day has been imputed to the 15th. If only the year is available, month and day have been imputed to July 1st.

Safety and Tolerability Results:

Safety data identified a tolerable and intolerable dose range of BMS-708163 in patients with mild-to-moderate AD (Table 3). Dosing with BMS-708163 at 100 mg and 125 mg/day was associated with significant intolerability and high discontinuation rates (primarily attributable to gastrointestinal [GI] and skin [rashes/pruritus] AEs). Dosing of BMS-708163 at 25 mg and 50 mg/day was associated with discontinuation rates similar to placebo. The overall incidence of SAEs was similar across placebo and all treatment groups.

Treatment-emergent AEs in the MedDRA SOCs of GI disorders and skin and subcutaneous tissue disorders increased with increasing dose. The incidence of GI AEs increased from 38% at 25 mg to 55%-56% at the 100-mg and 125-mg doses, and skin AEs increased from 10% at 25 mg to 63% at 125 mg.

The rate of treatment-emergent glycosuria also increased with increasing dose (from 34.1% at 25 mg to 62.5% at 125 mg; there were none in the placebo group). There were no mean serum glucose abnomalities or AEs associated with the glycosuria. In addition, treatment with BMS-708163 was not associated with decreases in glomerular filtration rate. Observed cases of new onset glycosuria resolved either on treatment (in 20% to 40% of patients) or by the first washout period laboratory assessment.

Treatment-emergent AEs and laboratory abnormalities of interest that occurred at greater rates in treatment groups compared to placebo include: glycosuria, asymptomatic MRI findings (e.g., vasogenic edema), GI ulcers, and non-melanoma skin cancer.

Routine Week 24 MRI safety scans revealed 3 cases of asymptomatic vasogenic edema (VE), 1 in the 25-mg group and 2 in the 50-mg group. Findings included gyral swelling, fluid-attenuated inversion-recovery cortical grey and leptomeningeal increased signal and white matter changes. One patient had evidence of VE at baseline which progressed radiologically at the Week 24 visit. Treatment-emergent VE completely resolved in 1 case at follow-up and partially resolved in the other 2 cases, which continue to be followed. All cases of VE have remained asymptomatic throughout the follow-up period.

Three patients in the 100-mg dose group reported a total of 4 GI ulcers; 1 additional patient reported an ulcer more than 30 days after the last dose of study medication. There were no AEs of ulcer reported in the other groups. Observed cases of ulcer occurred in patients with significant risk factors (including history of chronic reflux, concomitant antiplatlet use, prescribed NSAIDS, cholinesterase use, and positive culture for helicobacter.

Basal cell carcinoma was observed in 5% of patients in the 125-mg group and 0% in the other groups. The incidence of squamous cell carcinoma was 2% in the 125-mg group, 5% in each of the 25-mg and 50-mg groups, and 0% in the 100-mg and placebo groups. There were no observations of treatment emergent melanoma. All cases of non-melanoma skin cancers were clinically manageable by local treatment and no recurrences occurred. In addition, there were 2 cases of actinic keratosis (1 in the placebo group and 1 in the 25-mg group).

Table 3: Summary of Safety - Treatment-emergent Events During the Double-blind Phase, Safety Sample

	Number (%) of Patients				
	Placebo N = 42	**25 mg N = 42**	**50 mg N = 43**	**100 mg N = 41**	**125 mg N = 40**
Any AE	34 (81.0)	36 (85.7)	34 (79.1)	40 (97.6)	38 (95.0)
Related AE	10 (23.8)	20 (47.6)	20 (46.5)	24 (58.5)	27 (67.5)
Any SAE	8 (19.0)	7 (16.7)	7 (16.3)	6 (14.6)	6 (15.0)
AE leading to discontinuation	4 (9.5)	4 (9.5)	7 (16.3)	14 (34.1)	13 (32.5)
Deaths	0	0	0	0	0

Cognitive and Functional Outcome Results:

The primary objective of this study was the assessment of safety and tolerability. CN156013 was not adequately powered to determine efficacy in the treatment arms.

For the 25 mg and 50 mg/day treatment arms, clinical outcomes (ADAS-cog, CDR-SB, ADCS-ADL) were generally similar to placebo, although point estimates were typically favorable for BMS-708163 compared to placebo.

For the 100 mg and 125 mg/day treatment arms, several point estimates were consistent with worsening cognition (ADAS-cog) compared to placebo.

Outcomes in the placebo group did not reach the expected level of clinical deterioration for this study population. Review of the literature suggests a placebo decline over 6 months in mild to moderate AD of approximately 2 points on the ADAS-cog, and 3 to 4 points on the ADCS-ADL.[1] In CN156013, the estimated Week 24 declines in the placebo group were 0.3 points on the ADAS-cog and 0.9 points on the ADCS-ADL.

CSF Biomarkers:

CSF assay variability and small sample sizes limited the interpretation of CSF biomarker data. In the subset of patients who consented to lumbar punctures, statistically significant decreases at Week 24 trough values from baseline in Aβ38, Aβb40, and Aβ4 were observed. Using a repeated measures model, at 100 mg, there was a 28% decrease in Aβ38 ($P = 0.05$) assessed 24 hours after the last dose; changes in Aβ40 and Aβ42 were not significant. At 125 mg, there were decreases of 46% in Aβ38 ($P < 0.001$), 40% in Aβ40 ($P = 0.002$), and 34% in Aβ42 ($P = 0.034$). These decreases were consistent with those seen at Week 12. Changes in the 25- and 50-mg dose groups were not statistically significantly different from placebo as assessed approximately 24 hours after the last dose.

Compared to placebo, there were no statistically significant mean changes from baseline in Tau or p-Tau at any dose. Using a repeated measures model, at Weeks 12 and 24, declines in Tau were seen at all doses. For p-Tau, a mean increase was seen in the 25-mg group at Week 24 while there were declines in the other groups; none of these changes were statistically significant compared to placebo.

CONCLUSIONS:

- CN156013 identified safe and tolerable fixed doses of BMS-708163 for further clinical investigation in the mild to moderate AD population. Doses of 25 mg and 50 mg/day were relatively well tolerated with low discontinuation rates, while doses of 100 mg and 125 mg/day were associated with high discontinuation rates (primarily attributable to GI and skin AEs) and negative effects on cognition.
- Numerical reductions in levels of CSF biomarkers were observed across treatment groups, with robust lowering effects on trough amyloid concentrations at the 100-mg and 125-mg/day doses. Overall, trough amyloid biomarker data in the 25-mg and 50-mg dose groups were consistent with nonclinical and Phase 1 studies, suggesting a peak CSF amyloid reduction of 10% to 25% compared to baseline.
- AEs or laboratory abnormalities that were observed on treatment more often than placebo included glycosuria as well as low rates of non-melanoma skin cancer and asymptomatic MRI findings.
- The overall safety and tolerability profile of the 25-mg and 50-mg/day doses suggest their potential to test for efficacy in further clinical trials.
- Attributes of this study that limit conclusions include a small sample size, relatively short duration of treatment, and less than expected decline in the placebo group on clinical outcome measures.

DATE OF REPORT: 10-Jan-2011

REFERENCES

1 Schneider LS, Sano M. Current disease clinical trials: methods and placebo outcomes. Alzheimer's & Dementia. 2009; 5:388-397.