SYNOPSIS

Final Clinical Study Report for Study CN156018

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 Prodromal Alzheimer's Disease.

PURPOSE: The primary purpose of this study was to determine the safety, tolerability, and potential pharmacodynamic (PD) and pharmacokinetic (PK) effects of avagacestat (BMS-708163) versus placebo in subjects with prodromal Alzheimer's disease (AD) treated for at least 2 years. An interim analysis conducted after all subjects randomized to avagacestat had completed approximately 1 year of treatment showed no favorable efficacy trend and a lack of sufficient Aβ target engagement. Taken together, PD and biomarker results from the interim analysis did not justify further development of avagacestat in AD. Consequently, the clinical development program was terminated (30-Nov-2012) and the CN156018 study was discontinued approximately 15 months early (the last patient last visit was 09-Jul-2013).

This synoptic report summarizes results of available data for key efficacy, safety, and biomarker endpoints through early termination.

NUMBER OF SUBJECTS: A total of 1443 subjects were enrolled in the study (263 subjects were randomized and 1180 subjects were not randomized). Of the 263 randomized subjects, 132 subjects were assigned to avagacestat and 131 were assigned to placebo; 102 subjects who met clinical but not biomarker criteria for inclusion were followed in an observational cohort. The purpose of this observational cohort was to provide assay sensitivity regarding the biomarker criteria used to enrich the study population for subjects with underlying prodromal AD, and at greatest risk of progressing to dementia.

DISPOSITION, DEMOGRAPHICS AND OTHER PERTINENT BASELINE CHARACTERISTICS:

Subject disposition (Table 1), demographics (Table 2), baseline cognition evaluations (Table 3) and baseline summary of Aβ42 and Tau and number and percentage of randomized subjects meeting each CSF criteria (Table 4) are shown below.

Table 1: Subject Disposition: Enrolled Sample

Subject Status	Number of Subjects (%)		
	Placebo	BMS-708163	Total
Enrolled	NA	NA	1443
Not Randomized	NA	NA	1180
Observed Cohort	NA	NA	102
Randomized into Double-blind Phase	131	132	263
Discontinued from Double-blind Phase [a]	130 (99.2)	130 (98.5)	260 (98.9)
Lack of efficacy	6 (4.6)	4 (3.0)	10 (3.8)
Adverse event	14 (10.7)	45 (34.1)	59 (22.4)
Subject withdrew consent	16 (12.2)	13 (9.8)	29 (11.0)
Death	0	1 (0.8)	1 (0.4)
Lost to follow-up	2 (1.5)	1 (0.8)	3 (1.1)
Poor/non-compliance	3 (2.3)	0	3 (1.1)
Subject no longer meets study criteria	4 (3.1)	3 (2.3)	7 (2.7)
Subject request to discontinue study treatment	6 (4.6)	6 (4.5)	12 (4.6)
Administrative reason by sponsor	77 (58.8)	57 (43.2)	134 (51.0)
Other	2 (1.5)	0	2 (0.8)
Completed Double-blind Phase [a]	1 (0.8)	2 (1.5)	3 (1.1)

[a] Percentages are based on the number of subjects who were randomized.
NA - not applicable

Table 2: Demographics and Baseline Characteristics: Randomized Sample

	Statistic [a]	Placebo (N=131)	BMS-708163 (N=132)	Total (N=263)
Age (years)				
	n	131	132	263
	Mean (SD)	71.6 (7.78)	71.9 (7.63)	71.7 (7.69)
	Min-Max	49-89	52-90	49-90
Gender				
Male	n (%)	76 (58.0)	73 (55.3)	149 (56.7)
Female	n (%)	55 (42.0)	59 (44.7)	114 (43.3)
Race				
White	n (%)	130 (99.2)	125 (94.7)	255 (97.0)
Black/African American	n (%)	1 (0.8)	3 (2.3)	4 (1.5)
American Indian/Alaska Native	n (%)	0	1 (0.8)	1 (0.4)
Asian	n (%)	0	2 (1.5)	2 (0.8)
Other	n (%)	0	1 (0.8)	1 (0.4)
Body Mass Index (kg/m^2)				
	n	124	127	251
	Mean (SD)	25.00 (3.558)	26.24 (4.612)	25.62 (4.164)
	Median	25.05	26.10	25.60
	Min-Max	16.4-37.5	17.3-43.0	16.4-43.0
	Missing	7	5	12
Education (years)				
	n	131	132	263
	Mean (SD)	15.15 (3.482)	14.95 (3.549)	15.05 (3.510)
	Median	16.00	16.00	16.00
	Min-Max	7.0-26.0	6.0-24.0	6.0-26.0
APOE4 Status				
Two Apoe4 Alleles	n (%)	27 (20.6)	23 (17.4)	50 (19.0)
One Apoe4 Allele	n (%)	61 (46.6)	67 (50.8)	128 (48.7)
No Apoe4 Allele	n (%)	43 (32.8)	41 (31.1)	84 (31.9)
Missing	n (%)	0	1 (0.8)	1 (0.4)

[a] Percentages are based on the number of subjects who were randomized.
SD- standard deviation

Table 3: Baseline Cognition Evaluations: Randomized Sample

	Statistic	Placebo (N=131)	BMS-708163 (N=132)	Total (N=263)
MMSE	n	131	132	263
	Mean (SD)	27.1 (1.67)	27.0 (1.91)	27.0 (1.79)
	Median	27.0	27.0	27.0
	Min-Max	24-30	24-30	24-30
ADAS-cog 11 Item Total	n	131	132	263
	Mean (SD)	11.2 (4.50)	11.4 (4.80)	11.3 (4.65)
	Median	10.7	10.7	10.7
	Min-Max	3-22	3-28	3-28
ADCS-MCI-ADL	n	127	130	257
	Mean (SD)	45.7 (4.76)	44.6 (5.26)	45.2 (5.04)
	Median	46.0	45.0	46.0
	Min-Max	30-53	31-53	30-53
CDR-SB	n	131	132	263
	Mean (SD)	1.93 (0.966)	1.95 (1.027)	1.94 (0.995)
	Median	2.00	2.00	2.00
	Min-Max	0.5-5.0	0.5-4.5	0.5-5.0
FCSRT: Free Recall	n	127	124	251
	Mean (SD)	14.05 (7.570)	15.02 (8.581)	14.53 (8.083)
	Median	14.00	14.50	14.00
	Min-Max	2.0-42.0	1.0-43.0	1.0-43.0
FCSRT: Delayed Free Recall	n	127	124	251
	Mean (SD)	3.46 (3.500)	3.25 (3.285)	3.36 (3.390)
	Median	3.00	3.00	3.00
	Min-Max	0.0-13.0	0.0-13.0	0.0-13.0
FCSRT: Total Recall	n	127	124	251
	Mean (SD)	33.61 (11.397)	33.98 (11.561)	33.80 (11.457)
	Median	36.00	36.50	36.00
	Min-Max	6.0-48.0	5.0-48.0	5.0-48.0

N- number of subjects, MMSE- Mini Mental State Exam, ADAS-cog- Alzheimer's disease Assessment Scale - Cognitive Subscale, ADCS-MC-ADL- Alzheimer's disease Cooperative Study Activities of Daily Living, CDR-SB- Clinical Dementia Rating-Sum of Boxes, FCSRT- Free and Cued Selective Recall Reminding Test, SD- Standard Deviation
Note: Baseline MMSE data were collected at Screening.

Table 4: Baseline Summary of Aβ42 (Innogenetics) and Tau (Innogenetics) and Number and Percentage of Randomized Subjects Meeting Each CSF Criteria: Randomized Sample

	Statistic [a]	Placebo (N=131)	BMS-708163 (N=132)	Total (N=263)
Aβ42	n	131	132	263
	Mean (SD) (log scale) [b]	5.3 (0.34)	5.3 (0.32)	5.3 (0.33)
	Geometric Mean	206.7	197.7	202.2
	Min-Max	44-387	81-441	44-441
Tau	n	131	132	263
	Mean (SD) (log scale) [b]	4.8 (0.49)	4.8 (0.48)	4.8 (0.48)
	Geometric Mean	127.7	127.0	127.3
	Min-Max	36-571	34-414	34-571
Aβ42 < 200 pg/mL	n/N (%)	61/131 (46.6)	77/132 (58.3)	138/263 (52.5)
Tau/Aβ42 >= 0.39	n/N (%)	116/130 (89.2)	119/132 (90.2)	235/262 (89.7)
Aβ42 <200 pg/mL AND Tau/Aβ42 >= 0.39	n/N (%)	48/130 (36.9)	64/132 (48.5)	112/262 (42.7)

[a] Baseline values are first log-transformed; then summaries of mean baseline are calculated based on log-scale. The reported summary statistics are anti-log transformed into the original scale.
[b] Estimates in this row are on the log scale; estimates on the next row are back-transformed (exponentiated).
Note: Original baseline assay values at the time of randomization are used in this display.

SUMMARY OF SAFETY RESULTS:

Treatment at higher doses of 100 mg/day and 125 mg/day was associated with high discontinuation rates (primarily due to gastrointestinal adverse events and skin rashes), elevated AE rates, and worsening cognition which could potentially be due to adverse events or off target effects of the high dose range. Results from the completed Phase 2 CN156013 Mild-to-Moderate Alzheimer's disease study (based upon 209 randomized subjects) demonstrated that the 25 mg and 50 mg/day doses of BMS-708163 were generally well tolerated without evidence of cognitive worsening compared to placebo. Accordingly, as per Amendment 9, dated on 16-Sep-2010, the maximum daily dose of avagacestat in CN156018 was decreased from 125 mg to 50 mg QD due to tolerability and potential safety concerns. For the safety analyses, data from subjects were sub-grouped as Randomized before 16-Sep-2010 and Randomized on or after 16-Sep-2010 (Table 5). A total of 86 (65.2%) subjects in the avagacestat group and 87 (66.4%) subjects in placebo group were assigned to the higher dose 125 mg dose group prior to the protocol amendment dosing change (before 16-Sep-2010 time period). After the dosing change, 46 (34.8%) subjects in avagacestat group and 44 (33.6%) subjects in placebo group were randomized to the amended lower dose 50 mg QD (on or after 16-Sep-2010).

- No deaths occurred while subjects were actively dosed with avagacestat. Five deaths were reported for all enrolled subjects, 3 (2.3%) in avagacestat group after dosing had ceased, 1 (1.1%) in placebo group, and 1 (0.98%) in the observational cohort. The deaths in the 3 subjects randomized to avagacestat groups occurred after avagacestat dosing had ceased and were all characterized by the investigators as unrelated to study medication. The causes of death included: respiratory arrest (1 subject; 165 days after the last dose of avagacestat), small bowel obstruction (1 subject; 8 days after the last dose of avagacestat), and cardiopulmonary failure and dehydration (1 subject with left lymph node cancer; 136 days after the last dose of avagacestat). The cause of death in the 1 placebo treated subject was renal failure and in the 1 observational cohort subject was lung cancer.
- Serious adverse events across doses studied were reported for 49 (37.1%) subjects in the avagacestat group and 31 (23.7%) subjects in placebo group. The majority of SAEs occurred in subjects randomized prior to the 16-Sep-2010 protocol-specified dose reduction from 125 mg to 50 mg daily. The most frequent SAEs (reported for ≥ 2% of subjects) in the avagacestat group were basal cell carcinoma, squamous cell carcinoma of skin, and squamous cell carcinoma [8 (6.1%) subjects, each], prostate cancer [5 (3.8%) subjects], asthenia, subdural hematoma, vasogenic cerebral edema [3 (2.3%) subjects, each], and in the placebo group, basal cell carcinoma [5 (3.8%) subjects].
- Overall, 59 (22.4%) subjects discontinued from the study treatment due to AEs, 46 (34.8%) subjects in avagacestat group and 13 (9.9%) subjects in placebo group. The majority of discontinuations due to AEs occurred prior to the 16-Sep-2010 protocol-specified dose reduction from 125 mg to 50 mg daily.
- Adverse events (any grade) were reported for 126 (95.5%) subjects in the avagacestat group and 110 (84.0%) subjects in the placebo group. The majority of AEs occurred prior to the 16-Sep-2010 protocol-specified dose reduction from 125 mg to 50 mg daily.
- Overall, benign or malignant and unspecified skin lesions were reported for 23 (17.4%) subjects in the avagacestat group and 16 (12.2%) subjects in placebo group.

Table 5: Summary of Safety - Treatment-emergent Events During the Double-blind Phase Safety Sample

	Number of Subjects (%)					
	Before 16-Sep-2010		After 16-Sep-2010		Total	
	Placebo (N=87)	BMS-708163 (N=86)	Placebo (N=44)	BMS-708163 (N=46)	Placebo (N=131)	BMS-708163 (N=132)
Deaths[a]	1 (1.1)	0	0	3 (6.5)[b]	1 (7.6)	3 (2.3)
Serious Adverse Events	24 (27.6)	30 (34.9)	7 (15.9)	19 (41.3)	31 (23.7)	49 (37.1)
AEs Leading to Discontinuation	8 (9.2)	37 (43.0)	5 (11.4)	9 (19.6)	13 (9.9)	46 (34.8)
AEs	78 (89.7)	84 (97.7)	32 (72.7)	42 (91.3)	110 (84.0)	126 (95.5)
Skin related AEs	12 (13.8)	11 (12.8)	4 (9.1)	12 (26.1)	16 (12.2)	23 (17.4)

[a] One additional death in Observational Cohort. Subject [redacted], died of lung cancer (secondary to colon cancer) while on study.

[b] Deaths in the avagacestat group occurred after dosing and during the follow-up period. See section in text above for details

AE- adverse event

EFFICACY RESULTS:

CN156018 was not adequately powered to demonstrate efficacy. Assessment of clinical outcomes in this study, even as a secondary measure, is limited by the small sample size, the high intra-subject variability associated with the use of clinical rating scales, and the relatively short duration of study treatment due to study early termination. No consistent trend indicative of efficacy was observed between the avagacestat 50 mg/day and placebo groups based on ADAS-cog, CDR-SB, ADCS-MCI-ADL, and MMSE outcome measures.

BIOMARKER RESULTS:

CSF markers as Predictors of Progression to Dementia: Only subjects who met CSF inclusion criteria (cerebral spinal fluid [CSF] Aβ42 < 200 pg/mL or Total Tau/Aβ42 ratio of ≥ 0.39) in combination with clinical criteria indicative of prodromal AD at baseline were included in the randomized sample in this study. Subjects who met all other inclusion/exclusion criteria with the exception of the CSF criteria above were eligible to be followed in a non-randomized, observational cohort. Subjects in this non-randomized observational cohort served to provide prospectively collected CSF data permitting comparison of CSF values and progression to dementia rates over time. Once subjects in the observational cohort progressed to a diagnosis of dementia they were discontinued from the study. This procedure permitted testing the effectiveness of CSF Aβ42 and Total Tau as screening tools for enriching the AD study population.

Results from the study confirmed the utility of using CSF Aβ42 and Total Tau as screening tools to identify subjects more likely to progress to dementia. The percentage of subjects who progressed to dementia was observed as greater at 6 to 12 months in the randomized cohort selected with the clinical and CSF enrichment criteria. The rate of progression to dementia in the biomarker negative observational cohort (ie, subjects who did not meet CSF criteria for prodromal AD) was low and remained relatively flat through the 4 year observational period.

Volumetric brain MRI measurements: Volumetric MRI found no clinically relevant difference in hippocampal atrophy rates between the avagacestat and placebo groups. A small but numerically greater rate of whole brain volume loss, with a corresponding increase in ventricular volume for subjects randomized to avagacestat relative to placebo was observed. The clinical significance of these observations was unknown but previously reported with other amyloid lowering agents (AN1792 and bapineuzumab).

CSF biomarkers (Aβ40 and Aβ42): CSF biomarker data were analyzed across avagacestat dose groups. The degree of target engagement as measured by CSF Aβ40 and Aβ42 lowering was minimal. At Weeks 24 and 104, lowering of CSF Aβ40 by 10-15% was noted for all dose groups. At Weeks 24 and 104, the reduction of CSF Aβ42 was noted between 5-9%, which was not significantly different from placebo levels.

CONCLUSIONS:

- Avagacestat when dosed at 50 mg/day was better tolerated than the 125 mg dose in subjects with prodromal AD. No new safety issues emerged after the protocol reduced the dose to 50 mg.
- The 50 mg dose of avagacestat only demonstrated only minimal numerical reductions (10-15%) in Aβ40. No significant differences were observed in key clinical outcome measures across doses. There was no evidence of overall cognitive worsening associated with avagacestat administration on the key endpoints of CDR-SB, ADAS-cog, and ADCS-MCI-ADL.
- Progression to dementia was no different between avagacestat and placebo treated groups.
- Avagacestat did not improve hippocampal atrophy rates and there was a numerically greater rate of whole brain volume loss and increased ventricular volume in the avagacestat treated group. Similar decreases in brain volume have previously been reported with other amyloid-lowering treatments such as AN1792 and bapineuzumab.

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