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TRIPLE MONOAMINE REUPTAKE INHIBITOR

Final Clinical Study Report for Study CN162006

SYNOPTIC REPORT

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, ACTIVE-CONTROLLED STUDY OF THE EFFICACY AND SAFETY OF FLEXIBLY-DOSED BMS-820836 IN SUBJECTS WITH TREATMENT RESISTANT MAJOR DEPRESSION

Indication:	Depression
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THIS STUDY WAS CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE

Sponsor's Responsible Medical Officer:

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SYNOPSIS

Final Clinical Study Report for Study CN162006

TITLE OF STUDY: A Multicenter, Randomized, Double-Blind, Active-Controlled Study of the Efficacy and Safety of Flexibly-dosed BMS-820836 in Subjects with Treatment Resistant Major Depression

PURPOSE: The primary objective of the study was to demonstrate that 6 weeks of flexibly dosed BMS-820836 (0.5 - 2 mg/day) versus continuing a standard antidepressant treatment (duloxetine 60 mg/day) to which inadequate response had been shown, significantly reduces depressive symptoms in subjects with major depressive disorder (MDD). A reduction in depressive symptoms was quantified using the change in Montgomery Asberg Depression Rating Scale (MADRS) Total Score. The study was completed as planned. The primary objective was not achieved. This synoptic clinical study report (CSR) presents brief efficacy and safety results.

NUMBER OF SUBJECTS: The study included 4 phases: Screening (Phase A), Prospective Treatment (Phase B), Randomized Treatment (Phase C), and Washout (Phase D). Of the 887 subjects who enrolled and received prospective treatment with duloxetine 60 mg/day in Phase B, 346 subjects with inadequate response were randomly assigned to double-blind treatment in Phase C with either BMS-820836 (172 subjects, 1 subject was not treated) or continuing duloxetine (174 subjects).

DISPOSITION, DEMOGRAPHICS AND OTHER PERTINENT BASELINE CHARACTERISTICS: Disposition information is presented in Table 1 for subjects randomized in Phase C. 316 subjects (91.3% of those randomized; 90.1% in BMS-820836 and 92.5% in duloxetine) completed Phase C. Demographics and baseline characteristics were generally similar and balanced across treatment groups (Table 2). 81% of the randomized subjects were from North America. Mean baseline MADRS Total Score at randomization was 26.7 in the BMS-820836 treatment group and 26.9 in the duloxetine treatment group.'

Table 1: Subject Disposition for Subjects Randomized in Phase C

	BMS-820836	Duloxetine	Total
Subjects Randomized	172	174	346
Subjects Discontinued Phase C, N (%)	17 (9.9)	13 (7.5)	30 (8.7)
Reason for Discontinuation, N (%)			
Lack of efficacy	2 (1.2)	2 (1.1)	4 (1.2)
Adverse event	5 (2.9)	1 (0.6)	6 (1.7)
Subject request to discontinue study treatment	2 (1.2)	2 (1.1)	4 (1.2)
Subject withdrew consent	2 (1.2)	3 (1.7)	5 (1.4)
Death	1 (0.6)	0	1 (0.3)
Lost to follow-up	4 (2.3)	3 (1.7)	7 (2.0)
Poor/non-compliance	1 (0.6)	0	1 (0.3)
Pregnancy	0	1 (0.6)	1 (0.3)
Other	0	1 (0.6)	1 (0.3)
Subjects Completing Phase C	155 (90.1)	161 (92.5)	316 (91.3)

Table 2: Summary of Demographic Characteristics for Subjects Randomized in Phase C

	BMS-820836 N = 172	Duloxetine N = 174	Total N = 346
Age, years			
Mean	44.1	45.1	44.6
Min, Max	18, 65	18, 65	18, 65
Gender, N (%)			
Males	55 (32.0)	55 (31.6)	110 (31.8)
Females	117 (68.0)	119 (68.4)	236 (68.2)
Race, N (%)			
White	140 (81.4)	136 (78.2)	276 (79.8)
Black/African American	27 (15.7)	29 (16.7)	56 (16.2)
Asian	2 (1.2)	4 (2.3)	6 (1.7)
American Indian/Alaska Native	1 (0.6)	2 (1.1)	3 (0.9)
Native Hawaiian/Other Pacific Islander	0	1 (0.6)	1 (0.3)
Other	2 (1.2)	2 (1.1)	4 (1.2)

SUMMARY OF EFFICACY RESULTS: The adjusted mean change (SE) from end of Phase B in MADRS Total Score at Week 14 was -8.7 (0.661) for BMS-820836 and -8.1 (0.656) for duloxetine. The difference in means between the change in MADRS for BMS-820836 versus duloxetine was -0.6 (95% CI -2.3, 1.2).

SUMMARY OF SAFETY RESULTS: BMS-820836 (0.5 - 2 mg/day) was well tolerated in this study population of adults with treatment-resistant MDD, and no significant safety issues were observed.

Three deaths were reported during the study: accidental death during Phase C in a subject receiving BMS-820836 and two completed suicides (one during Phase B and one during Phase D) in subjects who received only duloxetine during their participation in the study.

During the Randomization Phase (Phase C), the following were observed for the safety sample:

- The most common AEs reported by at least 5% of subjects treated with BMS-820836 were headache (7.0%), nausea (7.0%), constipation (5.3%), and anxiety (5.3%). The most common AEs reported by at least 5% of subjects treated with duloxetine were headache (8.0%) and insomnia (5.2%).
- Eight subjects had SAEs: 5 subjects (2.9%) treated with BMS-820836 (cyst, atrial fibrillation, agitation, accidental death, and conversion, respectively) and 3 subjects (1.7%) treated with duloxetine (laceration, ureteric calculus, and accidental overdose, respectively).
- Six subjects discontinued from treatment due to AEs: 5 subjects (2.9%) treated with BMS-820836 [nausea and vomiting in 1 subject and atrial fibrillation, agitation, accidental death (noted above under deaths), and disturbance in attention in 1 subject each] and 1 subject (0.6%) treated with duloxetine (pregnancy).
- Small increases from end of Phase B were observed for adjusted mean heart rate and blood pressure values at Week 14 for the BMS-820836 treatment group; however, these changes were small and not clinically meaningful.

A summary of safety results in provided in Table 3.

Table 3: Summary of Safety Results for Subjects Treated in the Randomization Phase

	BMS-820836 N = 171	Duloxetine N = 174	Total N = 345
Deaths, N (%)	1 (0.6)	0	1 (0.3)
SAEs, N (%)	5 (2.9)	3 (1.7)	8 (2.3)
AEs leading discontinuation, N (%)	5 (2.9)	1 (0.6)	6 (1.7)
Any AE	98 (57.3)	117 (67.2)	215 (62.3)

CONCLUSIONS:

- The primary objective of CN162006 was not achieved. Flexibly dosed BMS-820836 (0.5 - 2 mg/day) was not superior to continuation of duloxetine in subjects with TRD. The efficacy of both drugs in this treatment-resistant MDD population was similar, with no statistically or clinically significant difference between BMS-820836 and duloxetine.
- BMS-820836 (0.5 - 2 mg/day) was well tolerated in the study population of adults with TRD, and no significant safety issues were observed.

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