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TRIPLE MONOAMINE REUPTAKE INHIBITOR

Final Clinical Study Report for Study CN162007

SYNOPTIC REPORT

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, ACTIVE-CONTROLLED, COMPARATIVE, FIXED-DOSE, DOSE RESPONSE STUDY OF THE EFFICACY AND SAFETY OF BMS-820836 IN PATIENTS WITH TREATMENT RESISTANT MAJOR DEPRESSION

Indication:	Depression
Phase:	2b
Study Initiation Date:	28-Jul-2011
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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 CN162007

TITLE OF STUDY: A Multicenter, Randomized, Double-blind, Active-Controlled, Comparative, Fixed-Dose, Dose Response Study of the Efficacy and Safety of BMS-820836 in Patients with Treatment Resistant Major Depression

PURPOSE: The purpose of the study was to demonstrate in subjects with treatment-resistant depression (TRD, based on retrospectively and prospectively defined inadequate response to antidepressant treatment in their current episode of major depressive disorder [MDD]) that fixed doses of BMS-820836 ≥ 1 mg/day showed superior reduction of the symptoms of depression versus continuation of the antidepressant treatment to which inadequate response was prospectively demonstrated. This study was completed. The primary endpoint was not met. This synoptic clinical study report presents brief efficacy and safety results.

NUMBER OF SUBJECTS: Of the 979 subjects who enrolled and received prospective treatment with duloxetine/escitalopram (Phase B), 502 subjects with inadequate response in Phase B were randomly assigned to double-blind treatment (Phase C) as follows: 51 subjects to BMS-820836 0.25 mg/day, 51 subjects to BMS-820836 0.5 mg/day, 102 subjects to BMS-820836 1 mg/day, 100 subjects to BMS-820836 2 mg/day, and 198 subjects to continuation of the Phase B antidepressant (duloxetine 60 mg/day or escitalopram 20 mg/day).

DISPOSITION, DEMOGRAPHICS AND OTHER PERTINENT BASELINE CHARACTERISTICS:

Disposition information is presented in Table 1 for subjects randomized in Phase C. Phase C was completed by 89.8% of those randomized (92.2%, 86.3%, 90.2%, and 89.0% in the BMS-820836 0.25 mg, 0.5 mg, 1 mg, and 2 mg arms, respectively, and 90.4% in the duloxetine/escitalopram arm). Demographics and baseline characteristics were generally similar and balanced across treatment groups at baseline (Table 2). 62% of the randomized subjects were from the US. Mean MADRS Total Score at randomization was 26.7, 27.0, 27.0, and 26.7 in the BMS-820836 0.25 mg, 0.5 mg, 1 mg, and 2 mg treatment groups, respectively, and 26.3 in the continuation treatment group.

Table 1: Subject Disposition for Subjects Treated in the Randomization Phase: Randomized Sample

	BMS-820836				Duloxetine 60 mg/ Escitalopram 20 mg	Total
	0.25 mg	0.5 mg	1 mg	2 mg		
Subjects Randomized/Treated	51	51	102	100	198	502
Subjects Discontinued Phase C, N (%)	4 (7.8)	6 (11.8)	10 (9.8)	9 (9.0)	18 (9.1)	47 (9.4)
Reason for Discontinuation, N (%)						
Lack of efficacy	0	1 (2.0)	1 (1.0)	2 (2.0)	2 (2.0)	6 (1.2)
Adverse event	0	1 (2.0)	2 (2.0)	2 (2.0)	3 (1.5)	8 (1.6)
Subject request to discontinue	0	2 (3.9)	0	1 (1.0)	1 (0.5)	4 (0.8)
Subject withdrew consent	1 (2.0)	1 (2.0)	0	0	6 (3.0)	8 (1.6)
Lost to follow-up	2 (3.9)	0	2 (2.0)	1 (1.0)	0	5 (1.0)
Poor/non-compliance	0	0	0	1 (1.0)	1 (0.5)	2 (0.4)
Pregnancy	0	0	1 (1.0)	0	0	1 (0.2)
Subject no longer met study criteria	0	0	3 (2.9)	1 (1.0)	4 (2.0)	8 (1.6)
Administrative reason by sponsor	0	1 (2.0)	1 (1.0)	0	1 (0.5)	3 (0.6)
Other	1 (2.0)	0	0	1 (1.0)	0	2 (0.4)
Subjects Completing Phase C, N (%)	47 (92.2)	44 (86.3)	92 (90.2)	89 (89.0)	179 (90.4)	451 (89.8)

Table 2: Summary of Demographic Characteristics for Subjects Treated in the Randomization Phase: Randomized Sample

	BMS-820836				Duloxetine 60 mg/ Escitalopram 20 mg N = 198	Total N = 502
	0.25 mg N = 51	0.5 mg N = 51	1 mg N = 102	2 mg N = 100		
Age, years						
Mean	44.8	43.6	46.1	49.0	46.8	46.6
Min, Max	20, 65	20, 65	20, 64	19, 65	19, 65	19, 65
Gender, N (%)						
Males	16 (31.4)	10 (19.6)	31 (30.4)	30 (30.0)	62 (31.3)	149 (29.7)
Females	35 (68.6)	41 (80.4)	71 (69.6)	70 (70.0)	136 (68.7)	353 (70.3)
Race, N (%)						
White	39 (76.5)	42 (82.4)	76 (74.5)	75 (75.0)	152 (76.8)	384 (76.5)
Black/African American	6 (11.8)	4 (7.8)	16 (15.7)	18 (18.0)	23 (11.6)	67 (13.3)
Asian	3 (5.9)	2 (3.9)	4 (3.9)	4 (4.0)	12 (6.1)	25 (5.0)
American Indian/ Alaska Native	0	0	0	0	1 (0.5)	1 (0.2)
Native Hawaiian/ Other Pacific Islander	1 (2.0)	0	0	0	2 (1.0)	3 (0.6)
Other	2 (3.9)	3 (5.9)	6 (5.9)	3 (3.0)	8 (4.0)	22 (4.4)

SUMMARY OF EFFICACY RESULTS

The adjusted mean change (SE) from End of Phase B in MADRS Total Score at Week 13 was -7.3 (0.83) and -6.6 (0.842) for BMS-820836 1 mg and 2 mg, respectively, and -6.9 (0.602) for the continuation group. No difference was observed between the combined 1 mg and 2 mg BMS-820836 dose groups and the continuation group (difference in mean change, -0.1 [95% confidence interval -1.7, 1.5]).

SUMMARY OF SAFETY RESULTS:

BMS-820836 (0.25 - 2 mg/day) was well tolerated in this study population of adults with TRD, and no significant safety issues were observed.

No deaths were reported in this study.

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

- The most common AEs reported by at least 10% of subjects treated with any dose of BMS-820836 were headache (8.9%-14.3% of subjects treated with BMS-820836) and nausea (5.5%-12.0% of subjects treated with BMS-820836). Among subjects treated with duloxetine/escitalopram continuation, headache and nausea were reported by 5.6% and 5.1% of subjects, respectively.
- One SAE (cholelithiasis) was reported by a subject in the duloxetine/escitalopram continuation group; no SAEs were reported for subjects treated with BMS-820836.

- Five subjects discontinued due to AEs: 3 (1.0%) subjects treated with BMS-820836 (tachycardia, suicidal ideation, and anxiety in 1 subject each) and 2 subjects (1.0%) treated with duloxetine/escitalopram continuation (depression and panic attack in 1 subject, nausea in 1 subject).
- Neuropsychiatric AEs were relatively infrequent and did not appear to be dose related.
- Dose-related mean increases from end of Phase B to Week 13 of Phase C in heart rate and systolic blood pressure were noted among subjects treated with BMS-820836.

A summary of safety results in provided in Table 3.

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

	BMS-820836				Duloxetine 60 mg/ Escitalopram 20 mg N = 196
	0.25 mg N = 50	0.5 mg N = 57	1 mg N = 101	2 mg N = 91	
Deaths, N (%)	0	0	0	0	0
SAEs, N (%)	0	0	0	0	1 (0.5)
AEs leading discontinuation, N (%)	0	0	2 (2.0)	1 (1.1)	2 (1.0)
Any AE	28 (56.0)	27 (47.4)	65 (64.4)	47 (51.6)	99 (50.5)

CONCLUSIONS:

The primary endpoint of Study CN162007 was not achieved; fixed doses of BMS-820836 ≥1 mg/day were not superior to continuation of duloxetine (SNRI) or escitalopram (SSRI) in subjects with TRD.

- The a priori hypothesized dose-efficacy relationships were not observed.
- BMS-820836 (0.5-2 mg/day) had antidepressant efficacy similar to continuation of duloxetine/escitalopram in patients with TRD.

BMS-820836 was well tolerated.

- Neuropsychiatric AEs were relatively infrequent and did not appear to be dose related.
- Dose-related increases were observed in heart rate and systolic blood pressure.

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