2. Synopsis

Abbreviated Clinical Study Report Synopsis: Study F1J-BI-SBCM

Title of Study: Duloxetine Versus Placebo in the Treatment of Community-Dwelling Women Aged 65 Years or Older with Stress or Stress-Predominant Mixed Urinary Incontinence	
Investigators: This multicenter study included 33 principal investigators.	
Study Centers: This study was conducted at 33 study centers in 7 countries.	
Publications Based on the Study: None at this time.	
Length of Study: 16 months Date first patient enrolled: 14 October 2005 Date last patient completed: 11 January 2007	**Phase of Development:** 4

Objectives: The primary objective was to assess the efficacy of duloxetine (20 mg twice daily [BID] for 2 weeks escalating to 40 mg BID) for up to 12 weeks in community-dwelling women with symptoms of stress urinary incontinence (SUI) or stress-predominant mixed urinary incontinence (S-MUI) compared with placebo, as measured by the percent change in total incontinence episode frequency (IEF) from baseline to endpoint using the 24-hour patient diary.

The secondary objectives were as follows:

To compare the efficacy of duloxetine 40 mg BID with that of placebo in the treatment of SUI and S-MUI as measured by:

- Absolute change in IEF from baseline to endpoint.
- Change in mean time between voids (MTBV) from baseline to endpoint.
- Percent change in the number of continence pads used (CPAD) per week from baseline to endpoint.
- Change in the Incontinence Quality of Life (I-QOL) total score and 3 subdomain scores from baseline to endpoint.
- Responder analysis based on the established within-treatment minimal clinically important difference (MCID) established for I-QOL. Based on this MCID, a "responder" is defined as a patient who had an increase in the I-QOL total score $\geq$6.3 points.
- Responder analysis based on percent change in IEF from baseline to endpoint ("responder" defined as $\geq$50% reduction in IEF from baseline to endpoint).
- Patient's rating of improvement using the Patient Global Impression of Improvement (PGI-I) questionnaire at endpoint.

To compare the efficacy of duloxetine 40 mg BID with that of placebo as measured by the percent change in IEF from baseline to endpoint using diaries in the subgroups of SUI and S-MUI separately.

To assess the impact of treatment with duloxetine 40 mg BID and placebo on the development of suicidal ideation using Question 9 of the Beck Depression Inventory®-II (BDI®-II).

To assess the impact of treatment with duloxetine 40 mg BID and placebo on cognition as measured by the change in the Modified Mini-Mental State Examination (3MS) score.

To assess the impact of treatment with duloxetine 40 mg BID and placebo as measured by changes in the BDI-II total score from baseline to endpoint.

To compare the safety of duloxetine 40 mg BID with placebo based on clinical laboratory values, change in vital signs, the occurrence and duration of treatment-emergent adverse events (TEAEs), and premature discontinuation of study due to AEs.

Study Design: Double-blind, stratified, randomized, parallel, placebo-controlled, outpatient, multicenter study.

Number of Patients:
Planned: Approximately 276 patients (138 active drug, 138 placebo)
Randomized: 265 (134 active drug, 131 placebo)
Completed: 226 (112 active drug, 114 placebo)

Diagnosis and Main Criteria for Inclusion: Community-dwelling women ≥65 years of age with symptoms of SUI or S-MUI for at least 3 consecutive months prior to Visit 1 including at least 7 incontinence episodes per week, and, for patients with MUI, at least 50% of the IEF must have been due to stress recorded on the stress/urge incontinence questionnaire (S/UIQ). Patients had to be ambulatory (able to use a toilet independently and without difficulty), have a post void residual (PVR) volume of ≤100 mL identified either by catheterization or ultrasounds within 15 minutes of a spontaneous void, and have no language or significant cognitive barriers (as determined by the 3MS score of >80).

Test Product, Dose, and Mode of Administration: Study Period II, 2-week dose escalation (Visit 3 to Visit 4): Duloxetine 40 mg/day, given orally BID as one 20-mg capsule in the morning and one 20-mg capsule in the evening.
Study Period II, 10-week active treatment (Visit 4 to Visit 7): Duloxetine 80 mg/day, given orally BID as one 40-mg capsule in the morning and one 40-mg capsule in the evening.
Study Period III, 2-week dose de-escalation (Visit 7 to Visit 8): Duloxetine 40 mg/day, given orally once daily as one 40-mg capsule.
From Visits 2 through 8 every patient took identical capsules (some containing placebo) BID.

Duration of Treatment: 12 weeks (Active Treatment Phase)

Reference Therapy, Dose, and Mode of Administration: Placebo, given orally, 2 capsules BID (Visit 2 through Visit 8).

Variables:
Efficacy:
- Percent change in total IEF from baseline to endpoint; absolute change in IEF from baseline to endpoint
- Change in MTBV from baseline to endpoint
- Percent change in the number of CPAD per week from baseline to endpoint
- Change in the I-QOL total score and 3 subdomain scores from baseline to endpoint

Other Variables:
- Frequency of Question 9 (suicidal ideation) scores of the BDI-II; changes in the BDI-II total score from baseline to endpoint
- Change in the 3MS score

Safety: Safety data included frequency and duration of AEs and premature discontinuation of study due to AEs, mean changes in and frequency of treatment-emergent abnormal values in vital signs and laboratory values. Blood pressure changes while supine, sitting, and standing were determined at every visit for surveillance of potential orthostatic hypotension development. Patients were assessed for evidence of emptying phase dysfunction at baseline by having a PVR urine volume measured.

Evaluation Methods:

Statistical: The planned statistical methods were to include: the intent-to-treat population in the summaries and analyses for patient disposition, demographics, and study medication exposure; all randomized and treated patients with a baseline and at least 1 postbaseline measurement in the efficacy analyses; and all randomized patients who received at least 1 dose of study medication in the safety analyses. During the study, several urge-predominant MUI (U-MUI) patients were inadvertently enrolled, randomized, and received treatment (protocol violations). For the purposes of this study report, all U-MUI patients were included in the demographics, disposition, and safety analyses; however, for the efficacy analyses, data from the U-MUI patients were summarized and presented independent of the efficacy analyses for the intended patient population (SUI and S-MUI patients).

The van Elteren's test was used to analyze the primary efficacy measure, percent change in IEF per week (IEF/week), where the stratification variables were baseline severity strata (<14 and ≥14 IEF/week), and symptoms of incontinence strata (SUI and S-MUI). The baseline was calculated as the weekly IEF average from all complete patient diary entries between Visit 1 and Visit 3; the endpoint was calculated as the weekly IEF average from all complete patient diary entries between Visit 3 and the last Active Treatment Phase visit prior to discontinuation. Percent changes in IEF/week in the subgroup S-MUI and in CPAD were analyzed in a similar manner. In the SUI subgroup, the normality test for percent change in IEF/week was valid and an analysis of variance (ANOVA) model was used with the same stratification variables and the same baseline and endpoint definition. An analysis of covariance (ANCOVA) model was used to analyze changes in MTBV with same stratification variables and the same baseline and endpoint definition.

For all other efficacy measures, baseline was the last nonmissing visit score obtained on or prior to Visit 3; the endpoint was the last nonmissing visit score obtained after Visit 3 and on or prior to the discontinuation visit during Active Treatment Phase. Changes in I-QOL (total and 3 subdomains) scores were analyzed using an ANCOVA model. The IEF/I-QOL responders and PGI-I analyses used the Cochran-Mantel-Haenszel statistic controlling for strata for symptoms of incontinence and strata for baseline severity (as in the primary analysis).

Analysis of 3MS and BDI-II scores used an ANCOVA model, while van Elteren's test was used to analyze the percent changes of IEF/week from baseline to endpoint (pooled diary approach) in subgroup BDI-II total <17 and BDI-II total ≥17.

The analysis of safety included all patients who were randomized and received treatment. Adverse events reported as reasons for discontinuation during the Active Treatment Phase were analyzed by treatment group using the Fisher exact test. Analysis of TEAEs, discontinuation-emergent adverse events (DEAEs; during the De-escalation/Discontinuation Phase), and treatment-emergent abnormal laboratory values used Fisher exact test. Mean changes in laboratory values and vital signs were evaluated by an ANOVA model.

Type III sums of squares were used from all ANOVA and ANCOVA models in order to test the treatment differences. All statistical tests were 2-sided and performed at a 0.05 significance level.

The planned sample size of 276 patients (approximately 138 patients per treatment group) provided at least 95% power to detect a treatment difference of 20% between duloxetine and placebo in the median percent change in IEF from baseline to endpoint using a 2-sided, 0.05 level van Elteren's test in the combined SUI and S- MUI groups.

Summary:

Disposition/Demographics:

- A total of 341 patients entered the study of which 265 were randomly assigned to treatment. A total of 232 patients completed the Active Treatment Phase and 226 patients completed De-escalation/Discontinuation Phase.
- The duloxetine and placebo groups were comparable regarding demographic and baseline characteristics and there were no significant differences between treatment groups.

Efficacy: In the primary analysis of percent change in IEF using the pooled analysis, duloxetine 40 mg BID demonstrated statistically significantly greater percent reduction in IEF compared with placebo. The median percent decrease in the number of IEF/week was 52.47% compared with 36.70% for the duloxetine and placebo groups, respectively ($p<.001$).

Secondary analyses found improvements to be statistically significantly different or to have numeric separation between duloxetine- and placebo-treated patients for the following secondary variables:

- Absolute change in IEF from baseline to endpoint was statistically significantly greater in the duloxetine-treated patients compared with placebo-treated patients; -8.85 and -5.51 ($p<.001$) for duloxetine and placebo, respectively.
- Percent change in IEF from baseline to endpoint (pooled diary analysis) in the S-MUI subgroup was statistically significantly greater in the duloxetine-treated patients than the placebo-treated patients (median percent change of 51.55% versus [vs] 32.74%, $p<.001$); however, in the SUI subgroup population, the percent change favored duloxetine, but no statistically significant difference was observed (median percent change of 52.95% vs 41.97% $p=.074$).
- Responder analyses: In the IEF responders analysis (pooled diary approach) significantly more duloxetine-treated patients were responders compared with placebo-treated patients (57.1% vs 35.2%, $p<.001$); in the I-QOL responder analysis, a greater percentage of duloxetine-treated patients were classified as responders compared with placebo-treated patients, but no statistically significant difference was observed (54.7% vs 47.5%, $p=.220$).
- Median percent change in the number of CPAD per week from baseline to endpoint favored duloxetine-treated patients (33.33% vs 16.55%, $p=.011$).
- Mean change in MTBV from baseline to endpoint were statistically significantly greater in the duloxetine-treated patients compared with placebo-treated patients (24.24 minutes vs 8.14 minutes, $p<.001$).
- Improvements (higher scores) in I-QOL total score and 3 subdomain scores from baseline to endpoint were statistically significantly greater for duloxetine patients compared with placebo patients (p-values $\leq .015$)
- Patient's rating of improvement using the PGI-I questionnaire and both modified PGI-I scales at endpoint: Duloxetine demonstrated significantly greater improvement compared with placebo ($p<.001$ for the full scale and for 1 of the modified scales; p-value of .003 for the other modified PGI-I scale).

Secondary analyses of change from baseline to endpoint specifically related to depression, thoughts of suicide, and cognition were as follows:

- The mean reduction in BDI-II score from baseline to endpoint demonstrated by each treatment group was minimal (mean changes of -0.67 and -0.45 for placebo and duloxetine, respectively) with no clinical relevance or statistically significant difference observed.
- Nearly all of patients, 122/123 placebo patients and 128/131 duloxetine patients, had no change in relation to suicidal ideation from baseline to endpoint (using the response to Question 9 of the BDI-II questionnaire). Of the 3 duloxetine-treated patients reporting a change from baseline related to thoughts of suicide, 2 reported worsening ("no thoughts" to "thoughts" of suicide) and 1 reported an improvement ("thoughts" to "no thoughts" of suicide); the 1 placebo-treated patient reporting a change from baseline to endpoint, reported a worsening from "no thoughts" to "thoughts" of suicide.

- The measurements for change in cognition based on the 3MS questionnaire demonstrated similar shifts by treatment groups from baseline to endpoint. For both treatment groups the majority of patients stayed the same at endpoint, reporting no cognition impairment.

Safety: A total of 10 patients reported 16 serious adverse events (SAEs). None of the SAEs were considered by the investigator to be related to study medication. There were no statistically significant differences between duloxetine and placebo in the percentage of discontinuations due to AEs during either the Active Treatment Phase or the De-escalation/Discontinuation Phase. There was no statistically significant difference between duloxetine-treated patients compared with placebo-treated patients in the overall incidence of TEAEs reported during the Active Treatment Phase. Individual TEAEs that were reported significantly more often and that occurred in ≥5% of patients in the duloxetine group were dry mouth, fatigue, constipation, and hyperhidrosis. Significantly more duloxetine-treated patients reported DEAEs than did patients in the placebo group (21.2% vs 9.2%, p=.012), although no statistically significant differences were observed for any individual event. Laboratory and vital sign data indicated no clinically relevant safety issues for duloxetine compared with placebo.

Conclusions: In summary, the superiority of duloxetine 40 mg BID over placebo in the treatment of women aged 65 or older with SUI or S-MUI has been demonstrated by statistically significant improvements in the primary and most secondary efficacy variables and analyses. Overall, the safety data from this study support the conclusion that duloxetine administered for up to 12 weeks (20 mg BID for 2 weeks escalating to 40 mg BID) for the treatment of SUI or S-MUI in women 65 years and older is well tolerated and has a satisfactory safety profile.

Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

3. Table of Contents for the Abbreviated Clinical Study Report