1 SYNOPSIS (CR002878)

Name of Sponsor/Company Ortho Urology, A Unit of Ortho-McNeil Pharmaceutical, Inc ***Name of Finished Product:*** Ditropan XL® ***Name of Active Ingredient:*** Oxybutynin chloride	***Individual Study Table Referring to Part of the Dossier*** ***Volume:*** ***Page:***	(For National Authority Use Only)

Title of Study: The effect of Ditropan XL® on vasomotor symptoms in healthy post-menopausal women: a double-blind placebo controlled pilot study

Investigators: Multiple, see Section 4, Investigators and Study Administrative Structure

Study Centers: Multiple, see Section 4, Investigators and Study Administrative Structure

Publication (reference): None

Study Period: ***Phase of Development:*** II
Date of first enrollment: April 26, 2004
Date of last completed: January 31, 2005

Objectives: The objective of this study was to evaluate the safety and efficacy of Ditropan XL® (oxybutynin chloride) for the treatment of vasomotor symptoms, also known as hot flushes, in healthy naturally postmenopausal women.

Methodology: This was a randomized, double-blind, multi-center, parallel group, placebo-controlled study evaluating the safety and efficacy of Ditropan XL on hot flushes in healthy naturally postmenopausal women. One hundred and forty-eight (148) women were randomized to Ditropan XL or placebo in a 1:1 ratio. The total duration of the study for each treatment group was approximately 98 days.

Subjects were women 40 to 65 years of age, in good health and postmenopausal. Subjects must have experienced natural menopause, been symptomatic and experienced a mean of seven or more moderate to severe hot flushes per day, based upon data obtained from the subject's completed diary for the 14 consecutive day period before they were randomized. Subjects must not have had a condition that required the use of an anticholinergic agent.

Subjects were seen for their Pre-Randomization Visit (Visit 1) at least 14 days before randomization to have a physical examination, medical history, hot flush history, vital signs and laboratory tests performed. Subjects also had daily diaries dispensed. Subjects used the diaries to record their hot flushes starting on Study Day -15. Diaries were collected and reviewed at each visit starting at Randomization Visit (Visit 2, Study Day -1).

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Subjects who met the eligibility criteria for this study returned for their Randomization Visit (Study Day -1). At this visit, subjects had vital signs taken, adverse events recorded, study medication dispensed and Quality of Life (QOL) questionnaires completed. The QOL questionnaires included: Sleep Quality Index questionnaire, Sleep Disruption Scale, Menopause-Specific QOL questionnaire, Short Form-36 Health Survey questionnaire, and Profile of Mood States (POMS) questionnaire. The subjects were instructed to start their study medication the morning after their Randomization Visit. The first day study drug was taken was defined as Study Day 1. In both treatment groups, subjects returned for follow-up visits between Study Days 8 to 14 (Visit 3), 22 to 28 (Visit 4), and 50 to 56 (Visit 5). The Final Study Visit (Visit 6) occurred between Study Days 78 to 84.

Safety was assessed by pre- and post-study physical examinations, laboratory analysis, adverse events and vital signs performed at various times throughout the study.

No interim analyses were performed.

Number of Subjects (planned and analyzed): The planned enrollment was approximately 140 women (70 subjects in the Ditropan XL group and 70 subjects in the placebo group). Data were available for 148 subjects from the Pre-Randomization Phase and 148 subjects from the Double-Blind Treatment Phase, all of whom were included in the safety analysis. Only the 145 subjects from the Double-Blind Treatment Phase who had an on-therapy visit were included in the intent-to-treat (ITT) efficacy analysis.

Diagnosis and Main Criteria for Inclusion: Healthy women between the ages of 40 and 65 years were eligible to participate. Subjects must have experienced natural menopause, been symptomatic and experienced a mean of seven or more moderate to severe hot flushes per day, based upon data obtained from the subject's completed diary for 14 consecutive days between the pre-randomization visit and Visit 2 (pre-randomization period).

Test Product, Dose and Mode of Administration, Batch Number: Study drug treatment was Ditropan XL 15 mg one oral tablet daily, Batch Number was: R12333.

Duration of Treatment: No treatment was administered during the Pre-Randomization Phase. During the Double-Blind Treatment Phase subjects received either Ditropan XL 15 mg or matching placebo. Subjects were instructed to take one tablet orally every day in the morning for 12 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number: Reference

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treatment consisted of one tablet/day of placebo, administered orally for 12 weeks. Placebo Batch Number was: R12334.

Criteria for Evaluation:

Efficacy: Efficacy assessments were obtained at Baseline and at Visits 2 through 6 of the Double-Blind Treatment Phase. The primary endpoints in this study were:

- Change in daily frequency of moderate to severe hot flushes from baseline to Week 12 (corresponding to visit 6 that was scheduled from day 78 to day 84); and
- Change in daily severity of all hot flushes from baseline to Week 12.

The secondary endpoints included:

- Change in daily frequency of moderate to severe hot flushes from baseline to Week 4;
- Change in severity of all hot flushes from baseline to Week 4;
- Change in daily composite score of moderate to severe hot flushes from baseline to Week 4 and Week 12;
- Change in daily frequency of all hot flushes from baseline to Week 4 and Week 12;
- Change in daily composite score of all hot flushes from baseline to Week 4 and Week 12;
- Frequency of moderate to severe hot flushes by weekly periods;
- Daily severity of all hot flushes by weekly periods;
- All scores from the Profile of Mood States (POMS);
- All scores from the Pittsburgh Sleep Quality Index (PSQI);
- All scores from the Menopause-Specific Quality of Life Questionnaire (MENQOL);
- All scores from the Short Form-36 Health Survey (SF-36);
- All scores from the Sleep Disruption Scale;
- Subject Global Assessment;
- Composite score of moderate to severe hot flushes by weekly periods;
- Proportion of subjects having a greater than 50% reduction in daily frequency of moderate to severe hot flushes from baseline to Week 4, and to Week 12;
- Proportion of subjects having a greater than 50% reduction in daily frequency of all hot flushes from baseline to Week 4, and to Week 12;
- Proportion of subjects having a greater than 50% reduction in daily severity of all hot flushes from baseline to Week 4, and to Week 12;
- Proportion of subjects having a greater than 50% reduction in daily composite score of moderate to severe hot flushes from baseline to Week 4, and to Week 12; and
- Proportion of subjects having a greater than 50% reduction in daily composite score of all hot flushes from baseline to Week 4, and to Week 12.

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Safety: Safety was assessed by pre- and post- study physical examinations, laboratory analysis, adverse events and vital signs including sitting pulse, blood pressure and weight.

Statistical Methods: All statistical tests were conducted at the two-sided, 5% significance level. For the primary endpoints, an analysis of covariance model was applied for treatment comparison with treatment and center as qualitative design factors. Baseline daily frequency of moderate to severe hot flushes was used as a covariate for the analysis of frequency of hot flushes at Week 12. Baseline daily severity of all hot flushes was used as a covariate for the analysis of the severity of hot flushes at Week 12.

All secondary endpoints were descriptively summarized for all time points at which they were assessed and at the final assessment. All secondary endpoints except weekly changes, Subject Global Assessment and the binomial proportion of subjects with 50% reduction scores were analyzed using analysis of covariance with baseline value as a covariate and treatment and center as qualitative design factors. Weekly changes in vasomotor scores were not analyzed inferentially. The five proportion scores of subjects with 50% reduction measures were analyzed using a Chi-square test. The Subject Global Assessment was analyzed using a Cochran-Mantel-Haenszel test with modified ridit scores and stratifying on center.

Average weekly scores for the frequency of moderate to severe hot flushes, the severity of all hot flushes and the composite scores of moderate to severe hot flushes were plotted.
The safety assessments included adverse events, clinical laboratory tests results, physical examination findings, vital signs and concomitant medications. The Safety population was used for all safety tables.

An analysis of covariance was used to analyze each final vital sign and final weight with the baseline value as a covariate and treatment and center as qualitative design factors.

Efficacy Results: A total of 148 subjects were randomized and 145 subjects were included in the ITT population; 73 subjects received Ditropan XL and 75 subjects received placebo. For the ITT population, mean age was 54.2 years, 81.4% were Caucasian, mean height was 162.5 cm and mean weight of the subjects was 70.7 kg. Mean FSH and TSH levels were 87.3 mIU/mL and 1.95 µIU/mL, respectively. Seventeen (11.7%) subjects were smokers and used on average 12.5 cigarettes per day. Overall, the age at last menstrual period was 48.0 years, the time from last menstrual period to randomization was 6.24 years, the mean age at start of hot flushes was 49.1 years, and the mean time from start of hot flushes to randomization was 5.18 years. Twenty-two (15.2%) subjects had a hysterectomy and the

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average age at hysterectomy was 40.3 years. The majority of subjects (80.7%) had not used hormonal therapy in the last 12 months.

A statistically significant decrease in the mean daily severity of all vasomotor symptoms (hot flushes) in subjects treated with Ditropan XL at Week 4 ($p<0.001$) and Week 12 ($p<0.001$) was observed compared to the placebo group, see Table 1.

Table 1. Change in Daily Severity of All Vasomotor Symptoms at Week 4 and Week 12 for Subjects in the Intent-to-Treat Population by Treatment Group

			Week 4[b]		Week 12[c]	
Treatment	Statistic	Baseline[a]	Change[d]	p-value[e]	Change[d]	p-value[e]
Ditropan XL	n	72	72		72	
(N=72)	Mean	2.47	-0.91	<0.001	-1.15	<0.001
	SD	0.275	0.832		0.952	
Placebo	n	73	73		73	
(N=73)	Mean	2.42	-0.22		-0.32	
	SD	0.356	0.435		0.704	

a: Daily severity is the sum of all mild hot flushes times 1, all moderate hot flushes times 2, and all severe hot flushes (including waking episodes) times 3 divided by the total number of hot flushes on that day. Baseline average is the average of all daily severity scores in the 14 days before the first dose of study medication.
b: Week 4 average is the average of all daily severity scores in the seven days before Visit 4 or the seven days including and before the last double-blind dose if subject withdrew before Visit 4.
c: Week 12 average is the average of all daily severity scores in the seven days before Visit 6 or the seven days including and before the last double-blind dose if subject withdrew before Visit 6.
d: Change is weekly score - baseline; negative value indicates a reduction in vasomotor symptoms and positive value indicates an increase in vasomotor symptoms.
e: p-value for the comparison of placebo versus Ditropan XL from analysis of covariance with treatment group and analysis center as qualitative factors and baseline daily severity as a covariate.

A statistically significant decrease in the frequency of moderate to severe vasomotor symptoms (hot flushes) in subjects treated with Ditropan XL at Week 4 ($p<0.001$) and Week 12 ($p<0.001$) was observed compared to the placebo group, see Table 2.

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Table 2. Change in Daily Frequency of Moderate to Severe Vasomotor Symptoms at Week 4 and Week 12 for Subjects in the Intent-to-Treat Population by Treatment Group

			Week 4[b]		Week 12[c]	
Treatment	Statistic	Baseline[a]	Change[d]	p-value[e]	Change[d]	p-value[e]
Ditropan XL	n	72	72		72	
(N=72)	Mean	11.87	-8.90	<0.001	-9.48	<0.001
	SD	4.436	4.980		5.137	
Placebo	n	73	73		73	
(N=73)	Mean	10.84	-4.06		-4.69	
	SD	3.983	3.916		4.761	

a: Total number of moderate and severe hot flushes (including waking episodes) divided by the number of daily diaries completed in the 14 days before the first dose of study medication.
b: Total number of moderate and severe hot flushes (including waking episodes) divided by the number of daily diaries completed in the seven days before Visit 4 or the last seven days including and before the last double-blind dose if subject withdrew before Visit 4.
c: Total number of moderate and severe hot flushes (including waking episodes) divided by the number of daily diaries completed in the seven days before Visit 6 or the last seven days including and before the last double-blind dose if subject withdrew before Visit 6.
d: Change is weekly score - baseline; negative value indicates a reduction in vasomotor symptoms and positive value indicates an increase in vasomotor symptoms.
e: p-value for the comparison of placebo versus Ditropan XL from analysis of covariance with treatment group and analysis center as qualitative factors and baseline daily frequency as a covariate.

Ditropan XL 15 mg was statistically significantly superior to placebo for those secondary endpoints that evaluated vasomotor symptoms (hot flushes) and their effects on sleep including: daily frequency of moderate to severe vasomotor symptoms and daily severity of all vasomotor symptoms at Week 4; frequency of all vasomotor symptoms at Week 12 and Week 4; composite score of moderate and severe hot flushes at Week 12 and Week 4; proportion of subjects with at least a 50% reduction in symptoms at Week 12 and Week 4; PSQI Sleep Disturbance, Subjective Sleep Quality and Global Sleep Index; Sleep Disruption; vasomotor subscale of MENQOL, and Subject Global Assessment.

A greater decline was apparent by Week 2 in the Ditropan XL group when compared to placebo for daily severity of all vasomotor symptoms by week, daily frequency of moderate to severe vasomotor symptoms by week, and daily composite score of moderate to severe vasomotor symptoms by week.

Ditropan XL was not statistically superior to placebo for those secondary endpoints that evaluated mood, mental functioning or quality of life measures not influenced by the reduction of vasomotor symptoms.

Safety Results: All study medications were well tolerated and no safety issues were

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identified. Overall, adverse events were reported by 79.5% of subjects in the Ditropan XL group and by 53.3% of subjects in the placebo group, p<0.001.

The most commonly reported adverse events were consistent with the known anticholinergic effects of Ditropan XL and included dry mouth, reported by 52.1% of subjects in the Ditropan XL group vs 5.3% in the placebo group (p<0.001), dyspepsia, reported by 12.3% of the subjects in the Ditropan XL group vs 1.3% in the placebo group (p=0.009), and diarrhoea, reported by 9.6% of the subjects in the Ditropan XL group and 0.0% in the placebo group, p=0.006.

A statistically significantly greater percentage of subjects in the Ditropan XL group reported urinary tract infection when compared to the percentage of subjects who reported this event in the placebo group (6.8% vs 0.0%, p=0.027). Other adverse events reported at a frequency of at least 5% in the Ditropan XL group were dysphagia (5.5% in the Ditropan XL group vs 0.0% in the placebo group, p=0.057) and nausea (5.5% in the Ditropan XL group vs 1.3% in the placebo group, p=0.206).

Two subjects in the Ditropan XL group reported serious adverse events unrelated to study drug administration. Ten (13.7%) subjects in the Ditropan XL group and three (4.0%) subjects in the placebo group withdrew from the study due to adverse events. No deaths were reported.

Conclusions:

- Ditropan XL 15 mg was statistically significantly superior to placebo for the treatment of vasomotor symptoms in healthy naturally postmenopausal women as demonstrated by both primary endpoints, daily frequency of moderate to severe vasomotor symptoms at Week 12 and daily severity of all vasomotor symptoms at Week 12.

- Ditropan XL 15 mg was statistically significantly superior to placebo for those secondary endpoints that evaluated vasomotor symptoms (hot flushes) including:
    - Daily frequency of moderate to severe vasomotor symptoms and daily severity of all vasomotor symptoms at Week 4
    - Frequency of all vasomotor symptoms at Week 12 and Week 4
    - Composite score of moderate and severe hot flushes at Week 12 and Week 4

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- Proportion of subjects with at least a 50% reduction in symptoms at Week 12 and Week 4
- PSQI Sleep Disturbance, Subjective Sleep Quality and Global Sleep Index
- Sleep Disruption
- Vasomotor subscale of MENQOL
- Subject Global Assessment

- A greater decline was apparent by Week 2 in the Ditropan XL group when compared to placebo for daily severity of all vasomotor symptoms by week, daily frequency of moderate to severe vasomotor symptoms by week, and daily composite score of moderate to severe vasomotor symptoms by week.

- No statistically significant differences were seen for any of the individual SF-36 Scales. However, a statistically significant improvement was observed in the Mental Component score in subjects treated with Ditropan XL versus placebo. A statistically significant improvement favoring the placebo group was observed in the Physical Component score.

- Ditropan XL was not statistically superior to placebo for those secondary endpoints that evaluated mood, mental functioning or quality of life measures not influenced by the reduction of vasomotor symptoms.

- All study medications were well tolerated and no safety issues were identified. The most commonly reported adverse events were consistent with the known anticholinergic effects of Ditropan XL and included dry mouth, dyspepsia, and diarrhoea.

- Two subjects in the Ditropan XL group reported serious adverse events unrelated to study drug administration. No serious adverse events were reported in the placebo group. Statistically significantly more subjects in the Ditropan XL group (ten or 13.7%) versus three (4.0%) subjects in the placebo group withdrew from the study because of adverse events. No deaths were reported.

Date of the Report: January 5, 2006

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