# 3 SYNOPSIS

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| **Name of sponsor: YAMANOUCHI Pharma America Inc** | Individual study table referring to part of the dossier<br><br>Volume:<br><br>Page: | (For national authority use only) |
| **Name of finished product: YM905 (solifenacin succinate)** | | |
| **Name of active ingredient: Solifenacin** | | |
| **Title of study:** | A randomized, double-blind, placebo-controlled, parallel-group, fixed-dose, multicenter study to assess efficacy and safety of daily oral administration of 10 mg YM905 (solifenacin succinate) versus placebo in male and female patients with overactive bladder | |
| **(International) Study No:** | 905-CL-013 | |
| **Investigators:** | [redacted] (replaced ); [redacted]; [redacted] (replaced ); [redacted]; | |
| **Study site(s) (United States):** | [redacted] | |
| **Publication (reference):** | None at the time of writing this report | |
| **Study period:** | Date first patient entered: 05 Feb 2001<br><br>Date of last patient's last observation: 17 Oct 2001 | |
| **Clinical Phase:** | 3 | |

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| **Objectives:** | Confirm the efficacy of YM905 versus placebo in reducing the number of micturitions per 24 hours in patients with overactive bladder and evaluate the safety and tolerability of YM905 in patients with overactive bladder. | |
| **Methodology:** | Phase 3, randomized, double-blind, parallel-group, fixed-dose, multicenter study of 10 mg YM905 versus placebo in the treatment of overactive bladder (frequency, urgency, and/or urge incontinence). The study consisted of a 2-week screening/washout period, a 12-week double-blind treatment period, and a 2-week post-treatment follow-up period. Patients who completed the study had the option to enter an open-label extension study. Patients visited the clinic at screening (Visit 1); baseline (Visit 2); after 4 weeks (Visit 3); 8 weeks (Visit 4); and 12 weeks (Visit 5) of double-blind treatment; and at the end of the follow-up period (for those patients who did not enter the extension study) (Visit 6). | |
| **Number of patients (planned and analyzed):** | The protocol called for enrolling 630 patients (315 to receive YM905 and 315 to receive placebo) to yield approximately 500 valid patients. A total of 672 patients were randomized (332 to placebo and 340 to YM905). All 672 patients took at least one dose of study drug and were included in the safety analysis and 615 (309 placebo and 306 YM905) were included in the full analysis set (FAS) for the evaluation of efficacy. The other 57 patients were excluded from the FAS because they had either no baseline or post-baseline diary entries. | |
| **Diagnosis and main criteria for inclusion:** | Symptoms of overactive bladder (urinary frequency with urgency and/or incontinence), age at least 18 years, an average of at least 8 micturitions/24 hours, and either an average of at least one urge urinary incontinence episode/24 hours or an average of at least one urinary urgency episode/24 hours, documented in a 3-day diary in the screening phase.<br><br>Patients with stress incontinence, mixed incontinence with a predominant stress component, or neurological cause for detrusor overactivity were excluded. | |

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| ***Test product***<br>**Dose:**<br>**Mode of administration:**<br>**Batch number:** | YM905<br>10 mg tablet, once daily<br>Oral<br>[redacted] | |
| **Duration of treatment:** | 12 weeks | |
| ***Reference therapy***<br>**Dose:**<br>**Mode of administration:**<br>**Batch number:** | Placebo<br>1 tablet, once daily<br>Oral<br>[redacted] | |
| ***Criteria for evaluation***<br><br>**Efficacy:**<br><br>[redacted] | The primary efficacy endpoint was mean change from baseline to endpoint in number of micturitions/24 h. Secondary efficacy endpoints were: mean change from baseline to endpoint in number of incontinence episodes/24 h; number of urgency episodes/24 h, mean volume voided/micturition, number of nocturnal voids/24 h, and number of nocturia episodes/24 h. These data were obtained from the patient diaries.<br><br>[redacted] | |
| **Safety:** | The safety of YM905 was evaluated on the basis of adverse events, clinical laboratory values (hematology, clinical chemistry, and urinalysis), vital signs, physical examinations, 12-lead electrocardiography (ECG), and post-void residual volume. | |

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| **Statistical methods:** | For continuous variables, descriptive statistics included the number of patients reflected in the calculation (n), mean, standard deviation (SD) for variables that describe the population (eg, demographic characteristics), or standard error (SE) for inferential variables (eg, efficacy and safety), median, minimum, and maximum. Frequencies and percentages were displayed for categorical data. | |
| **Summary of results:** | The number of patients completing the study was similar for the 2 treatment groups (83% for placebo 79% for YM905).<br><br>There were no notable imbalances between treatment groups in demographic characteristics. The study population was predominantly female and predominantly Caucasian with a mean age of 58 years. Approximately one third of the study population was 65 years or older, and 76 patients (11%) were 75 years or older. | |

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**Efficacy results:** In the FAS population, YM905 was statistically significantly superior to placebo in reducing the number of micturitions per 24 hours ($P < 0.001$) (primary efficacy endpoint). YM905 was also statistically significantly superior to placebo in reducing the number of incontinence episodes, urgency episodes, and in increasing volume voided per micturition (secondary endpoints). The superiority of YM905 over placebo in the reduction from baseline in micturitions per 24 hours was highly statistically significant when first observed at the Week 4 assessment and was maintained throughout the remainder of the double-blind treatment period.

## Overview of efficacy results at endpoint[a] (FAS, N = 615)

| | Placebo | | YM905 | | |
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| | **Baseline mean** | **Mean change from baseline (SE)** | **Baseline mean** | **Mean change from baseline (SE)** | ***P* value[b]** |
| **Primary efficacy endpoint** | | | | | |
| Number of micturitions/24 h | N = 309<br>11.5 | N = 309<br>-1.5 (0.15) | N = 306<br>11.7 | N = 306<br>-3.0 (0.15) | <0.001 |
| **Secondary efficacy endpoints** | | | | | |
| Number of incontinence episodes/24 h | N = 237<br>3.0 | N = 237<br>-1.1 (0.16) | N =225<br>3.1 | N =225<br>-2.0 (0.19) | <0.001 |
| Number of urgency episodes/24 h | N =306<br>7.2 | N =306<br>-2.5 (0.20) | N = 305<br>6.9 | N =305<br>-4.1 (0.20) | <0.001 |
| Volume voided per micturition | N = 308<br>190.3 | N = 308<br>2.7 (3.15) | N = 306<br>183.4 | N = 305<br>47.2 (3.79) | <0.001 |
| Number of nocturnal void episodes/24 h | N = 292<br>2.1 | N = 292<br>-0.5 (0.07) | N = 284<br>2.0 | N = 283<br>-0.7 (0.07) | 0.151 |
| Number of nocturia episodes/24 h | N = 279<br>1.7 | N = 279<br>-0.4 (0.06) | N = 268<br>1.6 | N = 267<br>-0.6 (0.06) | 0.097 |

Source: Appendix 14.2, Statistical Tables 12.1, 13.1, 14.1, 15.1, 16.1, 17.1

[a] Endpoint is the last available on-treatment visit on or before Week 12 (Visit 5).

[b] *P* value for testing the treatment difference, based on Van Elteren's method for treatment comparisons

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| **Safety results:** | More than half of the patients in both groups reported adverse events (59% for placebo and 69% for YM905). Most of the events were mild or moderate, but more events were rated severe in the YM905 group (13%) than in the placebo group (7%). Also the number of patients with adverse events judged possibly or probably related to study drug was higher for YM905 (52%) than for placebo patients (27%).<br>Serious adverse events were reported for 3 patients in the placebo group and 5 patients in the YM905 group. The percentage of patients with adverse events leading to discontinuation of study drug was higher for YM905 (11%) than for placebo (7%). One death was reported in a patient in the placebo group.<br>As expected, the majority of the events reported with YM905 were anticholinergic in nature, namely dry mouth (4% for placebo vs 27% for YM905) and constipation (3% for placebo vs 17% for YM905). The incidences of both dry mouth and constipation were significantly greater with YM905 than with placebo ($P < 0.001$). Dry mouth led to discontinuation of study drug in 1 placebo patient vs 12 (4%) for YM905. No placebo patient discontinued study drug because of constipation vs 12 (4%) for YM905. No other significant differences between treatment groups were noted with respect to individual adverse events.<br>YM905 had no influence on clinical laboratory parameters or vital signs. The electrocardiographic effects of YM905 reflect a statistically significant but very small (3.6 msec) mean relative prolongation of the QTc interval. Relative to baseline, 16 placebo and 24 YM905 patients had a QTc increase of 30 to 60 msec at Week 12. One YM905 female patient had a QTc of 510 msec at one observation (at Week 12). | |
| **Date of the report:** | 19 November 2002 | |