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# Long-term safety and efficacy of antimuscarinic add-on therapy in patients with overactive bladder who had a suboptimal response to mirabegron monotherapy: A multicenter, randomized study in Japan (MILAI II study)

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**Abbreviations & Acronyms**
DBP = diastolic blood pressure
ECG = electrocardiogram
EoT = end of treatment
FAS = full analysis set
HRQoL = health-related quality of life
IMI = imidafenacin
MIRA = mirabegron
MVV = mean volume voided
OAB = overactive bladder
OAB-q SF = overactive bladder questionnaire short form
OABSS = overactive bladder symptom score
PRO = propiverine
PVR = post-void residual
QTcF = QT interval corrected for heart rate by Fridericia's formula
SAF = safety analysis set
SBP = systolic blood pressure
SD = standard deviation
SOLI = solifenacin
TEAE = treatment-emergent adverse event
TOL = tolterodine

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**Objectives:** To evaluate the long-term safety (primary objective) and efficacy (secondary objective) of antimuscarinic add-on therapy in patients receiving mirabegron.

**Methods:** During a 2-week screening period, patients (aged ≥20 years, mirabegron treatment for ≥6 weeks, residual overactive bladder symptoms) received mirabegron 50 mg once daily. These patients were subsequently randomized to 52 weeks' treatment with mirabegron 50 mg/day plus an antimuscarinic (solifenacin 5 mg, propiverine 20 mg, imidafenacin 0.2 mg, or tolterodine 4 mg) with the potential to double the antimuscarinic dose (except for tolterodine) at week 8. Safety assessments included treatment-emergent adverse events, vital signs, 12-lead electrocardiograms, post-void residual volume, and laboratory evaluations. Efficacy was assessed using changes from baseline in overactive bladder symptom score total score; overactive bladder questionnaire short form score; micturitions, urgency episodes, urinary incontinence episodes, and urgency urinary incontinence episodes/24 h; mean volume voided per micturition; and number of night-time micturitions.

**Results:** Overall, 80.2% of patients (88.1% women, mean age 65 years) experienced at least one treatment-emergent adverse event, with similar rates for all treatments. The adverse events most commonly reported were dry mouth, nasopharyngitis, and constipation. No marked change was observed in systolic or diastolic blood pressure for any treatment, although pulse rate increased slightly in the mirabegron and propiverine, and mirabegron and tolterodine groups. For all treatments, significant improvements were observed in all efficacy parameters, including overactive bladder symptom score total and questionnaire short form scores.

**Conclusions:** Antimuscarinic add-on therapy is well tolerated and effective after initial treatment with mirabegron in patients with overactive bladder symptoms.

**Key words:** β3-adrenoreceptor agonist, antimuscarinic therapy, combination therapy, mirabegron, overactive bladder.

## Introduction

OAB is characterized by urinary urgency, with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia.[1] The syndrome is known to have a substantial impact on HRQoL and rates of depression.[2]

Although antimuscarinics are the cornerstone of pharmacotherapy for OAB symptoms, they are associated with specific anticholinergic side-effects, including dry mouth and

constipation.[3] Therefore, therapeutics that do not show these drawbacks could improve patient well being.

The β3-adrenoreceptor agonist, MIRA, has a distinct mechanism of action from antimuscarinics[4,5] and is therefore a potential alternative treatment for OAB symptoms. The efficacy and safety of MIRA has been proved in several phase III clinical trials.[6,7] Additional studies have shown that MIRA appears to be as effective as antimuscarinics and shows a lower incidence of drug-related TEAEs.[8,9] One-year persistence rates of up to 66.0% have been reported, with improved persistence and adherence versus antimuscarinic therapy.[10,11]

International urological associations recommend MIRA and antimuscarinics for treating patients with OAB symptoms.[12,13] However, even when favorable results are achieved in clinical studies, poor responses might be noted in the real-world setting.[14] Poor responders to initial treatment might achieve an improved outcome if they subsequently receive MIRA and an antimuscarinic in combination.

The favorable efficacy and safety profile of MIRA add-on therapy was shown in patients with OAB symptoms who did not respond to initial SOLI treatment in the MILAI and BESIDE studies.[15,16] Alternatively, if MIRA is used as first-line treatment, antimuscarinic add-on therapy could be considered in patients experiencing a suboptimal response to MIRA.

Previous combination studies either involved add-on treatment with MIRA[15,16] or concurrent use of both therapeutics[17,18] over a 12–16 week treatment period.[15–18] However, MIRA and antimuscarinics in combination might be used for long periods in clinical practice. Prolonged combination therapy might be associated with specific cumulative or delayed events and might have an additive effect on certain TEAEs. Therefore, the objectives of this MILAI II study were to evaluate the long-term safety (primary objective) and efficacy (secondary objective) of antimuscarinic add-on therapy to MIRA over 52 weeks in patients with OAB symptoms in Japan. The antimuscarinics investigated were the four main therapeutics used in Japan when the study was planned (SOLI, PRO, IMI, and TOL).

# Methods

## Study design

This was a multicenter, randomized, open-label, phase IV study in patients with OAB symptoms treated with MIRA (ClinicalTrials.gov: NCT02294396) that was carried out from October 2014 to September 2016 at 60 sites in Japan (Fig. 1).

The study was carried out in accordance with the Declaration of Helsinki and International Council for Harmonisation guidelines. The protocol was approved by the institutional review board for each site and all patients provided written informed consent.

Study duration was 54 weeks; a 2-week screening period and a 52-week treatment period. Eligible patients were aged ≥20 years, had received previous treatment with MIRA 50 mg for ≥6 weeks, and had residual OAB symptoms (OABSS total score ≥3 points, OABSS question 3 score ≥2 points). Full inclusion and exclusion criteria are in Table S1.

During screening, eligible patients received oral MIRA 50 mg once daily after breakfast. Using MIRA as a first choice therapeutic was based on daily clinical practice in Japan. Patients meeting the final eligibility criteria were subsequently randomized to receive a combination of MIRA 50 mg/day with SOLI 5 mg/day, PRO 20 mg/day, IMI 0.2 mg/day, or extended-release TOL 4 mg/day for 52 weeks (1:1:1:1 ratio). All treatments were taken orally once daily after breakfast, except for IMI which was also taken after dinner. At week 8, the dose of SOLI, PRO, or IMI could be doubled (if a patient had a poor response to the study drugs, was considered by the investigator to have no safety concerns, and agreed to the dose increase [TOL dose could not be increased because of prescribing restrictions]). If a TEAE developed after the dose increase, the dose could be reduced to the original level at the investigator's discretion. Subsequent dose re-escalations were not permitted.

## Study assessments

Safety (primary objective) was assessed throughout the study using TEAEs; vital signs, measured by patients on awakening and 6 h post-dose; 12-lead ECGs, including QTcF measurements; PVR volume; and laboratory evaluations.

Efficacy assessments (secondary objective) included change from baseline in OABSS total score; OAB-q SF score; micturitions, urgency episodes, urinary incontinence episodes, and urgency urinary incontinence episodes/24 h; MVV per micturition; and number of night-time micturitions. Patients completed a paper micturition diary for the 3 days before each site visit. The diary included data on the number of micturitions, urgency episodes and urgency urinary incontinence episodes, and volume voided per micturition. Efficacy assessments were carried out at baseline; weeks 4, 8, 12, 16, 28, 40, and 52; and at EoT, except for the OABSS (no week 40) and the OAB-q SF (only baseline; weeks 12, 28, and 52; and EoT).

## Statistical analysis

The target number of patients was determined to be 150 in each group (600 patients altogether). This took into account the estimated number of patients discontinuing from the study during treatment.[19] Randomization was carried out by the registration center (Bell Medical Solutions, Inc., Tokyo, Japan). Before treatment initiation, the site staff contacted the registration center to determine the treatment allocation.

Safety and demographic data were evaluated using the SAF (patients who received at least one dose of study drug). Efficacy data were evaluated using the FAS (patients who received at least one dose of study drug and provided data for at least one variable before and after treatment initiation).

Categorical data were summarized by the number and percentage of patients; descriptive statistics were used to analyze continuous variables. For efficacy variables, changes from baseline were evaluated using a one-sample *t*-test. Owing to the different nature of the antimuscarinics, it was judged that

 

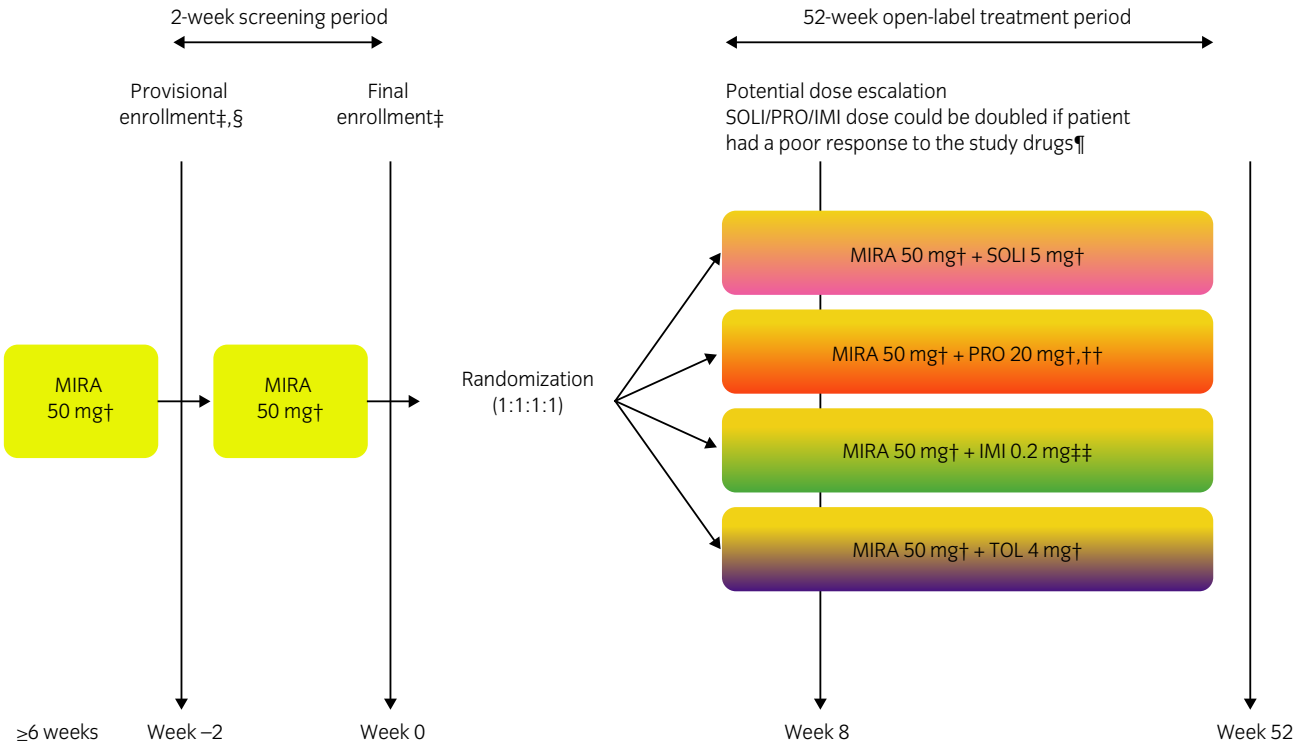


**Fig. 1** Study design. †Once daily. ‡Eligibility criteria were verified. §Informed consent was obtained. ¶Furthermore, the patient was considered by the investigator to have no safety concerns and agreed to the increased dose (in the event of a TEAE, the dose could be reduced to the initial dosage). ††If the PRO dose was doubled, patients received a 20-mg dose twice daily. ‡‡Twice daily (total daily dose shown).

direct statistical comparison of the effectiveness of the combination regimens was not appropriate.

## Results

### Study population

Overall, 730 patients entered screening, of whom 649 were randomized and 647 were included in both the SAF and the FAS (Fig. 2). Most patients were women (570 [88.1%] patients), with a mean age of 65 years, and a mean OAB duration of 77.2 months (Table 1). All treatment groups were generally similar regarding patient demographics and baseline characteristics.

At week 8, most patients (595 [92.0%] patients) did not have their antimuscarinic dose increased. Dose increases were administered to 15 (9.0%) MIRA and SOLI patients, 15 (9.3%) MIRA and PRO patients, and 22 (13.7%) MIRA and IMI patients. Seven (4.2%), four (2.5%), and five (3.1%) patients from the SOLI, PRO, and IMI groups, respectively, had their dose decreased back to the initial dosage.

### Safety

Overall, 519 (80.2%) patients experienced at least one TEAE (Table 2). Furthermore, 303 (46.8%) patients experienced at least one drug-related TEAE with similar incidences for all groups. Drug-related TEAEs leading to treatment withdrawal occurred in 47 (7.3%) patients; all occurrences were mild or moderate in severity.

In total, 28 (4.3%) patients reported at least one serious TEAE. Two serious TEAEs were considered by the investigator to be possibly drug-related. One patient treated with MIRA and PRO experienced a serious TEAE of atrial fibrillation, which resolved 10 days after treatment withdrawal. One patient treated with MIRA and TOL reported a serious TEAE of colitis ischemic, which resolved 23 days after treatment interruption and did not recur after restarting treatment. Another patient treated with MIRA and TOL died after a serious TEAE of acute respiratory distress syndrome. This event was considered to be unrelated to study treatment, as it occurred during drug withdrawal.

The most commonly reported TEAEs were dry mouth (163 [25.2%] patients), nasopharyngitis (140 [21.6%] patients), and constipation (107 [16.5%] patients). Compared with the other regimens, slightly higher incidences of dry mouth and constipation were observed in the MIRA and PRO and MIRA and SOLI groups, respectively. For drug-related TEAEs, the most commonly reported events were dry mouth (162 [25.0%] patients) and constipation (100 [15.5%] patients). Time-dependent changes were apparent in the prevalence of some TEAEs, with an overall higher prevalence in the earlier part of the study. In particular, dry mouth, constipation, dysuria, and residual urine volume increased were more commonly reported in the earlier stages of the study. There was no trend in the time onset of the other TEAEs (Table 3).

For pulse rate, no marked change from baseline to EoT was observed for any combination (Table 4). Over the treatment period, pulse rate remained constant in the MIRA and

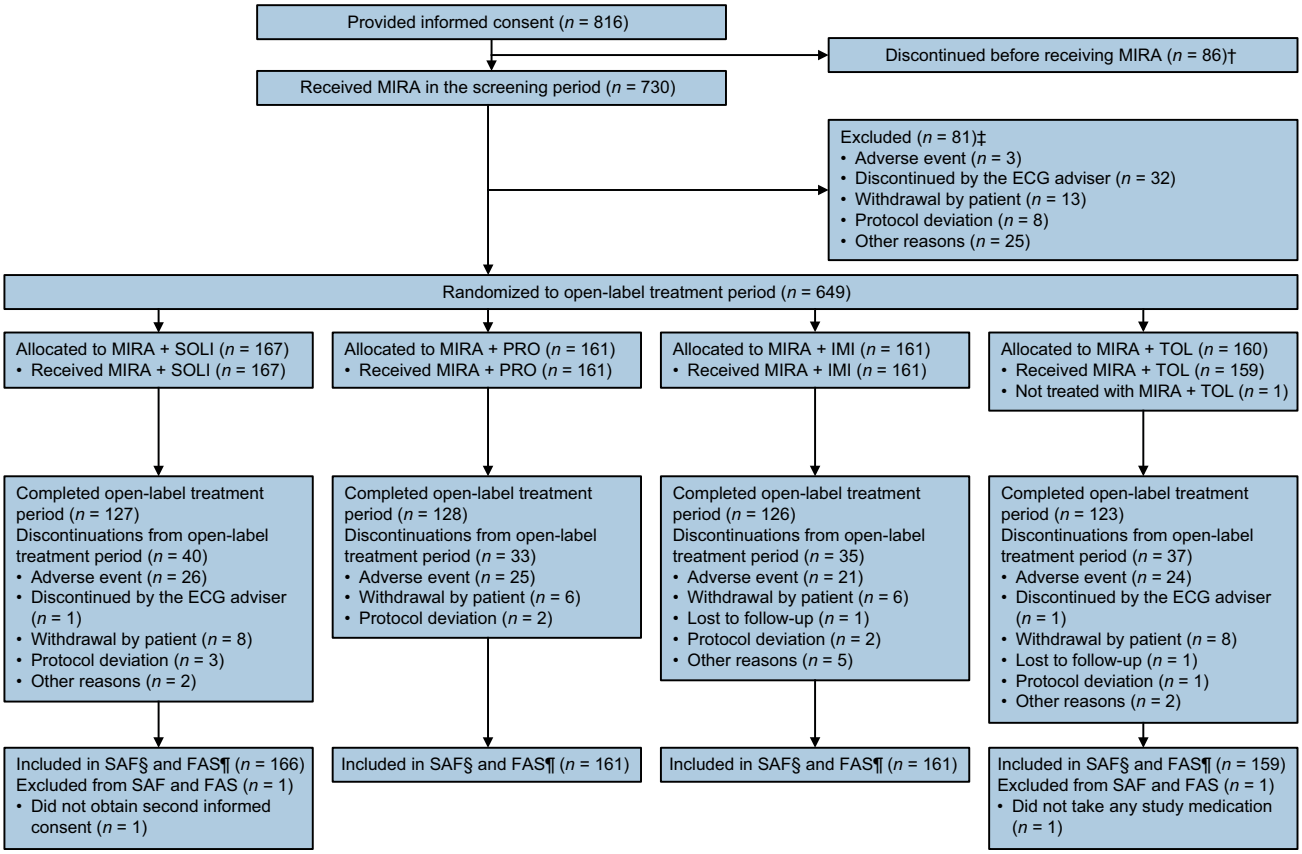


**Fig. 2** Patient disposition. †Patients who signed informed consent but discontinued before study treatment were defined as screen failures. ‡Patients who completed screening but discontinued before randomization were defined as run-in failures. §Patients who received at least one dose of study drug. ¶Patients who received at least one dose of study drug and provided data for at least one variable before and after treatment initiation.

SOLI and MIRA and IMI groups and increased slightly in the MIRA and PRO and MIRA and TOL groups (Fig. S1). No marked change from baseline to EoT was observed in SBP or DBP for any group (Figs S2,S3).

The QTcF interval remained reasonably constant from baseline to EoT and the observed changes ranged from −1.2 to 3.0 ms. No patient had a change in QTcF interval >60 ms from baseline to EoT. One MIRA and PRO patient had a QTcF interval >480 ms at week 16 (489 ms) and was discontinued from the study.

No notable change from baseline was found for PVR volume in any group. Drug-related residual urine volume increased was reported by 16 (2.5%) patients. No drug-related urinary retention was noted during the study. No clinically significant changes from baseline were found for any laboratory parameter.

### Efficacy

OABSS significantly improved by ≥3 points from baseline to EoT in all treatment groups (Table 5). From baseline to EoT, significant improvements of ≥10 points in both of the OAB-q SF measures (symptom severity score and total HRQoL score) were observed in all treatment groups. Significant improvements in OABSS and OAB-q SF were observed at the first time point evaluated (week 4 for OABSS, week 12 for OAB-q SF) and were maintained throughout the entire 52-week treatment period (Fig. 3).

For all combination treatments, significant improvements from baseline to EoT were observed in all parameters calculated from the micturition diary entries (micturitions, urgency episodes, urinary incontinence episodes, urgency urinary incontinence episodes, MVV, and night-time micturitions).

## Discussion

This is the first study to evaluate the long-term safety and efficacy of add-on therapy with four different antimuscarinics (SOLI, PRO, IMI, and TOL) in patients with OAB symptoms who were poor responders to initial MIRA treatment. Only one previous study has investigated MIRA in combination with a different antimuscarinic from SOLI; a small 8-week study of 30 patients with OAB symptoms evaluated the use of PRO add-on to MIRA therapy.[20]

In the present study, patients received add-on treatment with antimuscarinics after ≥8 weeks' treatment with MIRA (≥6 weeks before study start and 2 weeks during screening). The rationale for this time frame was based on findings from an efficacy analysis that found that clinical benefits can be achieved after just a few weeks of MIRA treatment.[21]

Add-on therapy with antimuscarinics was well tolerated over 52 weeks in the present study. Similar incidences of

**Table 1** Patient demographics and baseline characteristics

| Variable | MIRA + SOLI (*n* = 166) | MIRA + PRO (*n* = 161) | MIRA + IMI (*n* = 161) | MIRA + TOL (*n* = 159) | Total (*n* = 647) |
|---|---|---|---|---|---|
| Sex, *n* (%) | | | | | |
| Male | 20 (12.0) | 17 (10.6) | 15 (9.3) | 25 (15.7) | 77 (11.9) |
| Female | 146 (88.0) | 144 (89.4) | 146 (90.7) | 134 (84.3) | 570 (88.1) |
| Age in years | | | | | |
| Mean (SD, range) | 64.6 (9.4, 45–89) | 64.0 (9.3, 42–82) | 65.7 (8.7, 47–85) | 65.7 (10.0, 40–85) | 65.0 (9.4, 40–89) |
| Age group, *n* (%) | | | | | |
| <65 years | 86 (51.8) | 82 (50.9) | 65 (40.4) | 65 (40.9) | 298 (46.1) |
| ≥65 years | 80 (48.2) | 79 (49.1) | 96 (59.6) | 94 (59.1) | 349 (53.9) |
| Duration of OAB in months | | | | | |
| Mean (SD) [*n*] | 69.3 (68.2) [162] | 78.8 (88.9) [158] | 83.3 (94.2) [156] | 77.9 (85.8) [155] | 77.2 (84.7) [631] |
| Median (range) | 49.0 (1–334) | 53.0 (1–602) | 59.0 (1–545) | 55.0 (1–565) | 55.0 (1–602) |
| Status of urinary incontinence, *n* (%) | | | | | |
| Absent | 35 (21.1) | 25 (15.5) | 16 (9.9) | 22 (13.8) | 98 (15.1) |
| Urgency urinary incontinence | 99 (59.6) | 100 (62.1) | 96 (59.6) | 91 (57.2) | 386 (59.7) |
| Mixed urinary incontinence | 32 (19.3) | 36 (22.4) | 49 (30.4) | 46 (28.9) | 163 (25.2) |
| OAB severity (mean no. micturitions at baseline), *n* (%) | | | | | |
| <10 | 85 (51.2) | 76 (47.2) | 85 (52.8) | 79 (49.7) | 325 (50.2) |
| ≥10 to <15 | 74 (44.6) | 74 (46.0) | 64 (39.8) | 69 (43.4) | 281 (43.4) |
| ≥15 | 7 (4.2) | 11 (6.8) | 12 (7.5) | 11 (6.9) | 41 (6.3) |
| Urinary incontinence episodes at baseline, *n* (%) | | | | | |
| No | 75 (45.2) | 66 (41.0) | 58 (36.0) | 63 (39.6) | 262 (40.5) |
| Yes | 91 (54.8) | 95 (59.0) | 103 (64.0) | 96 (60.4) | 385 (59.5) |
| OABSS total score, mean (SD) | 7.4 (2.6) | 7.7 (2.5) | 7.8 (2.3) | 7.7 (2.3) | 7.6 (2.4) |
| OAB-q SF symptom severity score, mean (SD) | 32.81 (20.78) | 32.36 (21.23) | 32.92 (19.45) | 34.23 (22.60) | 33.08 (21.00) |
| OAB-q SF total HRQoL score, mean (SD) | 75.16 (17.65) | 77.36 (16.11) | 74.85 (18.50) | 75.37 (19.33) | 75.68 (17.91) |
| Micturitions/24 h, mean (SD) | 10.06 (2.59) | 10.37 (2.65) | 10.13 (2.92) | 10.20 (2.62) | 10.19 (2.69) |
| Urgency episodes/24 h, mean (SD) [*n*] | 3.26 (2.46) [153] | 3.12 (2.67) [148] | 3.27 (2.20) [150] | 3.15 (2.54) [148] | 3.20 (2.47) [599] |
| Urinary incontinence episodes/24 h, mean (SD) [*n*] | 1.62 (1.62) [91] | 1.59 (1.83) [95] | 1.47 (1.35) [103] | 1.55 (1.76) [96] | 1.56 (1.64) [385] |
| Urgency urinary incontinence episodes/24 h, mean (SD) [*n*] | 1.55 (1.47) [80] | 1.39 (1.45) [82] | 1.30 (1.16) [86] | 1.31 (1.62) [85] | 1.38 (1.43) [333] |
| MVV in mL/micturition, mean (SD) | 166.600 (50.404) | 170.064 (63.781) | 169.309 (50.324) | 167.542 (54.320) | 168.368 (54.839) |
| Night-time micturitions, mean (SD) [*n*] | 1.50 (0.96) [142] | 1.68 (1.08) [133] | 1.61 (1.29) [141] | 1.67 (1.04) [132] | 1.61 (1.10) [548] |

Data shown for the FAS (patients who received at least one dose of study drug and provided data for at least one variable before and after treatment initiation).

TEAEs, drug-related TEAEs, serious TEAEs, and the anticholinergic TEAEs of dry mouth and constipation were observed in all treatment groups. Although no monotherapy arms were included, the TEAE results from the present study are supported by findings from previous long-term Japanese clinical studies investigating the use of antimuscarinics as single agents (except for PRO, where there are a lack of long-term data).[22–25] For example, 45.8% of MIRA and SOLI patients reported a drug-related TEAE in the present study and incidences of 58.8% and 64.6% were reported in a multicenter, open-label study that involved the administration of SOLI monotherapy (5 or 10 mg) to 252 patients with OAB symptoms.[22] In terms of anticholinergic TEAEs, the incidence of drug-related constipation was 19.9% for the MIRA and SOLI group in the present study and incidences of 19.0% and 21.2% were reported in the Japanese SOLI monotherapy study.[22] Furthermore, the incidence of dry mouth as a TEAE was 25.2% for the MIRA and TOL group in the present study and an incidence of 33.5% was reported in a 12-month, open-label TOL monotherapy study.[23] Importantly, no new safety concerns were observed in the present study after the use of MIRA and antimuscarinics in combination versus previous long-term studies involving MIRA or antimuscarinics as monotherapies.[11,22–25] Additionally, no cumulative or delayed TEAEs were observed during the present study.

Compared with the present study, lower overall incidences of TEAEs have been reported in most previous SOLI and MIRA combination studies (78.9% *vs* 35.9–59.3%).[15,17,18] Regarding drug-related TEAEs, the overall incidence reported here (45.8%) was slightly higher than in earlier combination studies (17.7–44.4%).[15–18] In agreement with these findings, incidences of dry mouth (19.3%) and constipation (22.3%) after MIRA and SOLI in combination were slightly and noticeably higher, respectively, in the present study than in previous trials evaluating the safety of this combination regimen (dry mouth 5.9–17.3%, constipation 1.3–9.9%).[15,17,18] The variations in safety findings between the present study and previous SOLI and MIRA combination studies are likely due to differences in study design. The present study involved a longer treatment period than previous trials, had a different order of administration (e.g. MIRA was used as add-on therapy to SOLI in the BESIDE and MILAI studies[15,16]), and involved potential increases in the antimuscarinic dose at week 8 (patients receiving increased doses

**Table 2** TEAEs occurring during the course of the study

| | TEAE, *n* (%) | | | | | Drug-related TEAE, *n* (%) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | MIRA + SOLI (*n* = 166) | MIRA + PRO (*n* = 161) | MIRA + IMI (*n* = 161) | MIRA + TOL (*n* = 159) | Total (*n* = 647) | MIRA + SOLI (*n* = 166) | MIRA + PRO (*n* = 161) | MIRA + IMI (*n* = 161) | MIRA + TOL (*n* = 159) | Total (*n* = 647) |
| TEAE | 131 (78.9) | 135 (83.9) | 133 (82.6) | 120 (75.5) | 519 (80.2) | 76 (45.8) | 81 (50.3) | 72 (44.7) | 74 (46.5) | 303 (46.8) |
| Serious TEAE | 10 (6.0) | 4 (2.5) | 5 (3.1) | 9 (5.7) | 28 (4.3) | 0 | 1 (0.6) | 0 | 1 (0.6) | 2 (0.3) |
| TEAE leading to withdrawal of treatment | 23 (13.9) | 19 (11.8) | 16 (9.9) | 18 (11.3) | 76 (11.7) | 12 (7.2) | 17 (10.6) | 10 (6.2) | 8 (5.0) | 47 (7.3) |
| TEAE leading to death | 0 | 0 | 0 | 1 (0.6) | 1 (0.2) | 0 | 0 | 0 | 0 | 0 |
| TEAEs (≥3.0% for any group) | | | | | | | | | | |
| Dry mouth | 32 (19.3) | 51 (31.7) | 40 (24.8) | 40 (25.2) | 163 (25.2) | 31 (18.7) | 51 (31.7) | 40 (24.8) | 40 (25.2) | 162 (25.0) |
| Nasopharyngitis | 35 (21.1) | 39 (24.2) | 34 (21.1) | 32 (20.1) | 140 (21.6) | 0 | 0 | 0 | 0 | 0 |
| Constipation | 37 (22.3) | 27 (16.8) | 24 (14.9) | 19 (11.9) | 107 (16.5) | 33 (19.9) | 26 (16.1) | 23 (14.3) | 18 (11.3) | 100 (15.5) |
| Cystitis | 18 (10.8) | 13 (8.1) | 25 (15.5) | 10 (6.3) | 66 (10.2) | 0 | 0 | 4 (2.5) | 0 | 4 (0.6) |
| Dysuria | 8 (4.8) | 4 (2.5) | 3 (1.9) | 7 (4.4) | 22 (3.4) | 8 (4.8) | 4 (2.5) | 3 (1.9) | 7 (4.4) | 22 (3.4) |
| Back pain | 3 (1.8) | 5 (3.1) | 6 (3.7) | 4 (2.5) | 18 (2.8) | 0 | 0 | 0 | 0 | 0 |
| Contusion | 4 (2.4) | 6 (3.7) | 3 (1.9) | 5 (3.1) | 18 (2.8) | 0 | 0 | 0 | 0 | 0 |
| Abdominal discomfort | 7 (4.2) | 4 (2.5) | 4 (2.5) | 2 (1.3) | 17 (2.6) | 5 (3.0) | 2 (1.2) | 3 (1.9) | 2 (1.3) | 12 (1.9) |
| Eczema | 5 (3.0) | 2 (1.2) | 6 (3.7) | 4 (2.5) | 17 (2.6) | 1 (0.6) | 0 | 1 (0.6) | 0 | 2 (0.3) |
| Gastroesophageal reflux disease | 2 (1.2) | 6 (3.7) | 4 (2.5) | 5 (3.1) | 17 (2.6) | 0 | 3 (1.9) | 2 (1.2) | 3 (1.9) | 8 (1.2) |
| Residual urine volume increased | 6 (3.6) | 8 (5.0) | 1 (0.6) | 2 (1.3) | 17 (2.6) | 6 (3.6) | 7 (4.3) | 1 (0.6) | 2 (1.3) | 16 (2.5) |
| Pharyngitis | 6 (3.6) | 4 (2.5) | 4 (2.5) | 2 (1.3) | 16 (2.5) | 0 | 0 | 0 | 0 | 0 |
| Dermatitis contact | 3 (1.8) | 7 (4.3) | 2 (1.2) | 2 (1.3) | 14 (2.2) | 0 | 0 | 0 | 0 | 0 |
| Gastroenteritis | 3 (1.8) | 2 (1.2) | 5 (3.1) | 2 (1.3) | 12 (1.9) | 0 | 0 | 0 | 0 | 0 |
| Osteoarthritis | 5 (3.0) | 2 (1.2) | 3 (1.9) | 2 (1.3) | 12 (1.9) | 0 | 0 | 0 | 0 | 0 |
| Gastritis | 2 (1.2) | 5 (3.1) | 4 (2.5) | 0 | 11 (1.7) | 0 | 1 (0.6) | 2 (1.2) | 0 | 3 (0.5) |
| Headache | 5 (3.0) | 4 (2.5) | 0 | 2 (1.3) | 11 (1.7) | 2 (1.2) | 2 (1.2) | 0 | 1 (0.6) | 5 (0.8) |
| Vomiting | 1 (0.6) | 2 (1.2) | 5 (3.1) | 3 (1.9) | 11 (1.7) | 0 | 0 | 1 (0.6) | 0 | 1 (0.2) |
| Dizziness | 2 (1.2) | 5 (3.1) | 0 | 3 (1.9) | 10 (1.5) | 1 (0.6) | 1 (0.6) | 0 | 1 (0.6) | 3 (0.5) |
| Dental caries | 0 | 6 (3.7) | 3 (1.9) | 0 | 9 (1.4) | 0 | 0 | 0 | 0 | 0 |
| ECG QT prolonged | 1 (0.6) | 2 (1.2) | 5 (3.1) | 1 (0.6) | 9 (1.4) | 1 (0.6) | 2 (1.2) | 4 (2.5) | 1 (0.6) | 8 (1.2) |
| Osteoporosis | 1 (0.6) | 5 (3.1) | 2 (1.2) | 1 (0.6) | 9 (1.4) | 0 | 0 | 0 | 0 | 0 |
| Cataract | 1 (0.6) | 1 (0.6) | 1 (0.6) | 5 (3.1) | 8 (1.2) | 0 | 0 | 0 | 0 | 0 |
| Dyspepsia | 0 | 5 (3.1) | 1 (0.6) | 1 (0.6) | 7 (1.1) | 0 | 2 (1.2) | 1 (0.6) | 1 (0.6) | 4 (0.6) |

Data shown for the SAF (patients who received at least one dose of study drug).

**Table 3** First onset of TEAEs (≥3.0% for any group) by time interval

| | Time interval (days) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ≥1 to <7 (*n* = 647) | ≥7 to <14 (*n* = 645) | ≥14 to <28 (*n* = 642) | ≥28 to <56 (*n* = 628) | ≥56 to <84 (*n* = 598) | ≥84 to <112 (*n* = 579) | ≥112 to <196 (*n* = 561) | ≥196 to <280 (*n* = 538) | ≥280 to <365 (*n* = 517) | ≥365 (*n* = 129) |
| Overall TEAEs, *n* (%) | 96 (14.8) | 38 (5.9) | 51 (7.9) | 107 (17.0) | 57 (9.5) | 33 (5.7) | 63 (11.2) | 46 (8.6) | 25 (4.8) | 3 (2.3) |
| Dry mouth | 70 (10.8) | 14 (2.2) | 9 (1.4) | 30 (4.8) | 17 (2.8) | 9 (1.6) | 7 (1.2) | 6 (1.1) | 1 (0.2) | 0 |
| Nasopharyngitis | 1 (0.2) | 4 (0.6) | 11 (1.7) | 17 (2.7) | 14 (2.3) | 6 (1.0) | 24 (4.3) | 37 (6.9) | 26 (5.0) | 0 |
| Constipation | 13 (2.0) | 13 (2.0) | 17 (2.6) | 20 (3.2) | 17 (2.8) | 8 (1.4) | 13 (2.3) | 4 (0.7) | 2 (0.4) | 0 |
| Cystitis | 1 (0.2) | 0 | 3 (0.5) | 4 (0.6) | 10 (1.7) | 5 (0.9) | 17 (3.0) | 17 (3.2) | 8 (1.5) | 1 (0.8) |
| Dysuria | 6 (0.9) | 2 (0.3) | 2 (0.3) | 4 (0.6) | 4 (0.7) | 1 (0.2) | 2 (0.4) | 1 (0.2) | 0 | 0 |
| Back pain | 0 | 0 | 0 | 1 (0.2) | 2 (0.3) | 1 (0.2) | 6 (1.1) | 5 (0.9) | 3 (0.6) | 0 |
| Contusion | 0 | 0 | 2 (0.3) | 3 (0.5) | 2 (0.3) | 0 | 3 (0.5) | 5 (0.9) | 3 (0.6) | 0 |
| Abdominal discomfort | 1 (0.2) | 3 (0.5) | 0 | 1 (0.2) | 3 (0.5) | 1 (0.2) | 4 (0.7) | 2 (0.4) | 2 (0.4) | 0 |
| Eczema | 2 (0.3) | 0 | 0 | 4 (0.6) | 1 (0.2) | 1 (0.2) | 4 (0.7) | 3 (0.6) | 2 (0.4) | 0 |
| Gastroesophageal reflux disease | 2 (0.3) | 1 (0.2) | 0 | 0 | 2 (0.3) | 1 (0.2) | 2 (0.4) | 7 (1.3) | 2 (0.4) | 0 |
| Residual urine volume increased | 1 (0.2) | 0 | 3 (0.5) | 10 (1.6) | 2 (0.3) | 0 | 1 (0.2) | 0 | 0 | 0 |
| Pharyngitis | 1 (0.2) | 0 | 2 (0.3) | 0 | 2 (0.3) | 1 (0.2) | 3 (0.5) | 4 (0.7) | 3 (0.6) | 0 |
| Dermatitis contact | 0 | 0 | 0 | 2 (0.3) | 1 (0.2) | 1 (0.2) | 5 (0.9) | 5 (0.9) | 0 | 0 |
| Gastroenteritis | 1 (0.2) | 1 (0.2) | 1 (0.2) | 0 | 0 | 0 | 4 (0.7) | 3 (0.6) | 2 (0.4) | 0 |
| Osteoarthritis | 0 | 0 | 1 (0.2) | 1 (0.2) | 0 | 0 | 5 (0.9) | 2 (0.4) | 3 (0.6) | 0 |
| Gastritis | 0 | 0 | 0 | 2 (0.3) | 0 | 1 (0.2) | 3 (0.5) | 3 (0.6) | 2 (0.4) | 0 |
| Headache | 3 (0.5) | 0 | 1 (0.2) | 1 (0.2) | 2 (0.3) | 2 (0.3) | 1 (0.2) | 0 | 1 (0.2) | 0 |
| Vomiting | 0 | 1 (0.2) | 1 (0.2) | 0 | 2 (0.3) | 4 (0.7) | 3 (0.5) | 0 | 0 | 0 |
| Dizziness | 1 (0.2) | 0 | 0 | 1 (0.2) | 1 (0.2) | 1 (0.2) | 3 (0.5) | 2 (0.4) | 1 (0.2) | 0 |
| Dental caries | 0 | 0 | 0 | 2 (0.3) | 2 (0.3) | 0 | 1 (0.2) | 2 (0.4) | 2 (0.4) | 0 |
| ECG QT prolonged | 0 | 0 | 0 | 4 (0.6) | 1 (0.2) | 1 (0.2) | 3 (0.5) | 0 | 0 | 0 |
| Osteoporosis | 0 | 0 | 1 (0.2) | 0 | 1 (0.2) | 1 (0.2) | 2 (0.4) | 2 (0.4) | 2 (0.4) | 0 |
| Cataract | 0 | 0 | 0 | 1 (0.2) | 0 | 0 | 5 (0.9) | 1 (0.2) | 1 (0.2) | 0 |
| Dyspepsia | 1 (0.2) | 2 (0.3) | 0 | 1 (0.2) | 0 | 0 | 1 (0.2) | 2 (0.4) | 0 | 0 |

Data shown for the SAF (patients who received at least one dose of study drug).

experienced higher incidences of TEAEs than those receiving lower doses [data not shown]).

Previous investigations have indicated that MIRA might marginally increase heart rate,[6,7] although the clinical relevance of this is unknown. In the present study, no clinically significant differences in pulse rate from baseline to EoT were observed. For the MIRA and SOLI and MIRA and IMI groups, pulse rate remained constant over the treatment period. Increases in pulse rate of 2.86–3.19 b.p.m. and 2.11–3.40 b.p.m. were observed in the MIRA and PRO and MIRA and TOL groups, respectively. Previous clinical investigations have noted similar increases after the use of PRO (4.4 b.p.m.) or TOL (1.5–2.0 b.p.m.) as single agents.[26,27] Administration of the combination regimens did not have a notable effect on SBP or DBP. Supporting this finding, the results of the phase II Symphony study found that negligible changes in blood pressure were observed after the use of SOLI and MIRA in combination.[17]

Unanticipated cardiovascular events were not observed in the present study. This finding is supported by the results of a subanalysis from the BESIDE study, which found no synergistic effect on cardiovascular safety after SOLI and MIRA combination therapy.[28] No clinically significant changes in QTcF intervals from baseline to EoT were observed, regardless of the combination treatment administered, and no patient experienced a QTcF interval >500 ms or a change in QTcF interval from baseline to EoT of >60 ms. Similar findings have been reported in both the BESIDE and MILAI studies.[16,28]

Statistically significant improvements in efficacy were observed in the present study for all parameters investigated after the administration of all four combination regimens. In this study, clinically significant improvements in OABSS and OAB-q SF were observed at EoT after the use of combination treatments (changes of ≥3 and ≥10 points denote clinically significant improvements in OABSS and OAB-q parameters, respectively).[29,30] For both OABSS and OAB-q SF, statistically significant differences from baseline were observed from the first time point evaluated and improvement was maintained throughout the entire treatment period. The significant improvements shown in OABSS and OAB-q SF in the present study are supported by the SOLI and MIRA combination results from the short-term MILAI study.[16]

Significant improvements from baseline were observed in all of the efficacy parameters that were assessed using data from the patient micturition diary. Similar findings have been observed in previous SOLI and MIRA combination studies.[15–18] Overall, similar levels of improvement were

**Table 4** Vital sign, ECG, and PVR volume results

| Variable | MIRA + SOLI (*n* = 166) | MIRA + PRO (*n* = 161) | MIRA + IMI (*n* = 161) | MIRA + TOL (*n* = 159) |
|---|---|---|---|---|
| Vital signs | | | | |
| Pulse rate in b.p.m. on awakening, mean (SD) [*n*] | | | | |
| Baseline | 70.07 (8.15) [166] | 69.15 (8.19) [161] | 69.17 (7.25) [160] | 68.51 (8.15) [159] |
| EoT | 70.68 (7.55) [159] | 72.35 (9.68) [155] | 69.26 (6.76) [157] | 70.64 (8.39) [156] |
| Change from baseline to EoT | 0.68 (4.95) [159] | 3.19 (6.54) [155] | 0.09 (5.74) [156] | 2.11 (5.20) [156] |
| Pulse rate in b.p.m. 6 h post-dose, mean (SD) [*n*] | | | | |
| Baseline | 74.91 (8.80) [166] | 73.87 (9.16) [160] | 74.56 (8.08) [161] | 74.09 (8.68) [159] |
| EoT | 74.93 (7.99) [159] | 76.74 (10.09) [155] | 73.22 (7.94) [157] | 77.55 (9.25) [156] |
| Change from baseline to EoT | 0.17 (6.25) [159] | 2.86 (6.62) [154] | −1.27 (6.67) [157] | 3.40 (6.86) [156] |
| SBP in mmHg on awakening, mean (SD) [*n*] | | | | |
| Baseline | 128.91 (16.03) [166] | 129.75 (17.22) [161] | 127.21 (16.34) [160] | 129.22 (16.41) [159] |
| EoT | 126.91 (15.02) [159] | 126.86 (15.87) [155] | 126.28 (15.24) [157] | 126.65 (14.62) [156] |
| Change from baseline to EoT | −1.60 (11.56) [159] | −2.88 (9.08) [155] | −0.86 (9.64) [156] | −2.31 (10.14) [156] |
| SBP in mmHg 6 h post-dose, mean (SD) [*n*] | | | | |
| Baseline | 125.45 (13.52) [166] | 125.44 (13.99) [160] | 125.20 (14.35) [161] | 127.15 (13.74) [159] |
| EoT | 125.06 (13.24) [159] | 123.78 (13.11) [155] | 123.45 (14.03) [157] | 124.66 (13.40) [156] |
| Change from baseline to EoT | −0.46 (10.53) [159] | −1.55 (9.27) [154] | −1.64 (9.23) [157] | −2.35 (9.86) [156] |
| DBP in mmHg on awakening, mean (SD) [*n*] | | | | |
| Baseline | 80.65 (9.14) [166] | 80.45 (10.36) [161] | 79.08 (10.04) [160] | 79.40 (9.82) [159] |
| EoT | 79.40 (8.83) [159] | 79.46 (9.96) [155] | 78.52 (9.45) [157] | 78.72 (9.52) [156] |
| Change from baseline to EoT | −0.90 (6.48) [159] | −1.00 (6.07) [155] | −0.64 (6.31) [156] | −0.54 (6.81) [156] |
| DBP in mmHg 6 h post-dose, mean (SD) [*n*] | | | | |
| Baseline | 78.03 (8.38) [166] | 77.67 (9.23) [160] | 77.30 (9.32) [161] | 77.85 (8.76) [159] |
| EoT | 77.33 (8.40) [159] | 77.12 (9.24) [155] | 75.55 (9.13) [157] | 78.12 (8.89) [156] |
| Change from baseline to EoT | −0.54 (6.48) [159] | −0.56 (6.25) [154] | −1.79 (5.92) [157] | 0.33 (7.17) [156] |
| ECGs | | | | |
| QTcF in ms, mean (SD) [*n*] | | | | |
| Baseline | 418.5 (17.4) [164] | 419.2 (16.9) [161] | 416.4 (17.3) [160] | 415.4 (15.6) [158] |
| EoT | 420.5 (16.6) [164] | 418.0 (16.7) [160] | 416.0 (17.5) [160] | 418.5 (15.9) [159] |
| Change from baseline to EoT | 1.8 (11.6) [162] | −1.2 (10.8) [160] | −0.4 (12.8) [159] | 3.0 (10.6) [158] |
| Absolute QTcF at EoT, *n* (%) | | | | |
| ≤450 ms | 158 (96.3) | 157 (98.1) | 158 (98.8) | 155 (97.5) |
| >450 to ≤480 ms | 6 (3.7) | 2 (1.3) | 2 (1.3) | 4 (2.5) |
| >480 to ≤500 ms | 0 | 1 (0.6) | 0 | 0 |
| Change in QTcF from baseline to EoT, *n* (%) | | | | |
| <0 ms | 70 (43.2) | 86 (53.8) | 77 (48.4) | 54 (34.2) |
| >0 to ≤30 ms | 91 (56.2) | 73 (45.6) | 80 (50.3) | 104 (65.8) |
| >30 to ≤60 ms | 1 (0.6) | 1 (0.6) | 2 (1.3) | 0 |
| PVR volume | | | | |
| PVR volume in mL, mean (SD) [*n*] | | | | |
| Baseline | 11.02 (15.43) [166] | 10.43 (17.07) [161] | 9.74 (14.35) [161] | 9.10 (14.41) [159] |
| EoT | 19.31 (43.18) [164] | 17.27 (34.86) [160] | 14.26 (26.04) [161] | 15.04 (36.68) [159] |
| Change from baseline to EoT | 8.17 (39.42) [164] | 6.83 (32.20) [160] | 4.52 (23.51) [161] | 5.94 (35.83) [159] |

Data shown for the SAF (patients who received at least one dose of study drug).

**Table 5** Change from baseline to EoT in efficacy parameters

| Variable | MIRA + SOLI (*n* = 166) | MIRA + PRO (*n* = 161) | MIRA + IMI (*n* = 161) | MIRA + TOL (*n* = 159) |
|---|---|---|---|---|
| OABSS total score, mean (SD) [*n*] | −3.9 (2.7)* [164] | −4.1 (2.6)* [160] | −3.9 (2.6)* [161] | −4.2 (2.8)* [159] |
| OAB-q SF symptom severity score, mean (SD) [*n*] | −18.92 (18.42)* [160] | −18.99 (19.14)* [159] | −18.89 (18.11)* [159] | −21.28 (20.99)* [154] |
| OAB-q SF total HRQoL score, mean (SD) [*n*] | 14.38 (14.98)* [160] | 12.46 (13.89)* [159] | 13.99 (16.72)* [159] | 14.36 (17.51)* [154] |
| Micturitions/24 h, mean (SD) [*n*] | −2.18 (1.96)* [159] | −1.89 (2.08)* [155] | −1.75 (2.09)* [157] | −1.91 (2.22)* [156] |
| Urgency episodes/24 h, mean (SD) [*n*] | −2.03 (2.55)* [147] | −2.24 (2.41)* [143] | −2.04 (2.19)* [149] | −2.07 (2.23)* [146] |
| Urinary incontinence episodes/24 h, mean (SD) [*n*] | −1.25 (1.48)* [87] | −1.18 (1.59)* [92] | −1.03 (1.08)* [101] | −1.15 (1.52)* [93] |
| Urgency urinary incontinence episodes/24 h, mean (SD) [*n*] | −1.20 (1.32)* [76] | −1.12 (1.33)* [80] | −0.91 (0.93)* [85] | −1.05 (1.59)* [82] |
| MVV in mL/micturition, mean (SD) [*n*] | 40.004 (45.095)* [159] | 38.691 (46.429)* [155] | 32.854 (44.481)* [157] | 40.683 (46.566)* [156] |
| Night-time micturitions, mean (SD) [*n*] | −0.47 (0.91)* [137] | −0.38 (0.88)* [131] | −0.48 (0.93)* [139] | −0.48 (0.88)* [130] |

*$P < 0.001$ *vs* baseline. Data shown for the FAS (patients who received at least one dose of study drug and provided data for at least one variable before and after treatment initiation).

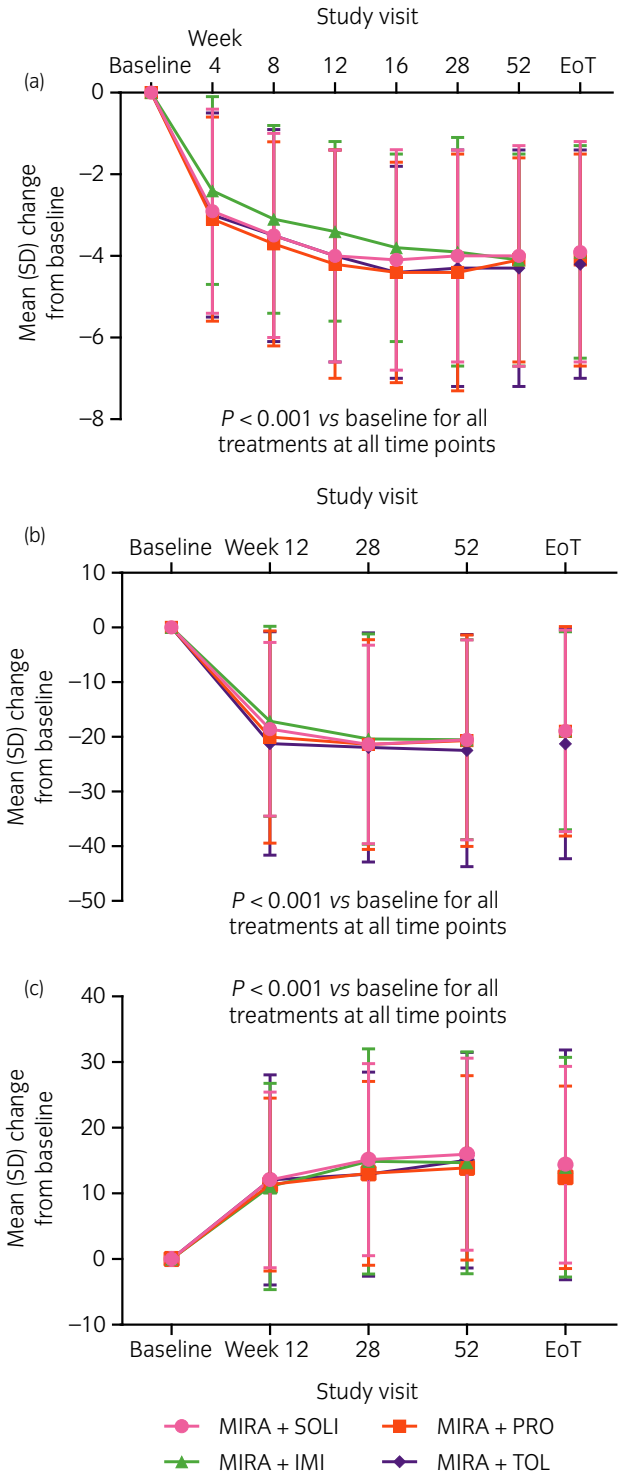


**Fig. 3** Mean change from baseline at each visit in (a) OABSS total score, (b) OAB-q SF symptom severity score, and (c) OAB-q SF total HRQoL score. Data shown for the FAS (patients who received at least one dose of study drug and provided data for at least one variable before and after treatment initiation).

observed for all four combination therapies evaluated, regardless of the efficacy parameter investigated.

Although novel data were obtained, the present study does have some limitations. As 1-year treatment with placebo is ethically problematic, a placebo arm was not included. Additionally, no monotherapy treatment arms were investigated. The trial was open label; a potential source of patient- and physician-associated bias. In addition, 88.1% of the patients were women; a higher proportion than in previous SOLI and MIRA combination studies (66.4–83.9%)[15–18] and post-marketing Japanese investigations (50.5–53.2%).[11,14] Furthermore, we believe that an antimuscarinic drug should be added to a patient's therapeutic regimen if they experience an insufficient response to treatment with MIRA. Alternatively, if a patient does not respond to MIRA, their treatment should be switched from MIRA to an antimuscarinic. However, patients who do not respond to MIRA treatment are infrequently encountered within the clinical setting. Therefore, in the present study, add-on therapy with antimuscarinics was selected for use during the 52-week treatment period. However, useful clinical data could be obtained if additional investigations are carried out to compare the efficacy and safety of switching to antimuscarinics with that of MIRA plus antimuscarinic add-on therapy.

In conclusion, the present study is the first to show the safety and efficacy of long-term antimuscarinic add-on therapy in patients with OAB symptoms after initial MIRA treatment. The findings indicate that antimuscarinic add-on treatment might become a potential clinical option for treating patients with OAB symptoms after the use of first-line MIRA therapy. Results of additional studies examining the long-term use of MIRA and antimuscarinics in combination are awaited with interest.

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## Conflict of interest

OYa, HK, YH, YI, MT, ON, MG, MY, and OYo received advisory board fees; OYa, HK, YH, YI, MT, ON, MG, MY, OYo, and NS received consultancy fees; OYa, HK, YH, YI, MT, ON, MG, MY, OYo, and NS received editorial assistance; HK and YI received grants; OYa, HK, YH, YI, MT, ON, MG, MY, OYo, and NS received lectureship fees; and MG received study funding from Astellas Pharma Inc. AO, TH, AK, and KK are employees/former employees of Astellas Pharma Inc. OYa received grants from Asahi Kasei Pharma Corporation. MT and MG received consultancy fees; HK, YI, and MG received grants; and YI, MT, MG, MY, and OYo received lectureship fees from Daiichi Sankyo Company, Limited. OYo received consultancy fees and lectureship fees from GlaxoSmithKline K.K. OYa received consultancy fees and grants; OYa and OYo received lectureship fees from

Hisamitsu Pharmaceutical Co., Inc. MT and MY received advisory board fees; YI, MT, MG, MY, OYo, and NS received consultancy fees; HK and YI received grants; YI, MT, ON, MG, MY, OYo, and NS received lectureship fees; and HK received speaker fees from Kissei Pharmaceutical Co., Ltd. HK, MT, MG, MY, and OYo received advisory board fees; HK, MT, MG, MY, and OYo received consultancy fees; YI and MG received grants; and OYa, YI, MT, MG, MY, OYo, and NS received lectureship fees from KYORIN Pharmaceutical Co., Ltd. YI received consultancy fees; HK and YI received grants; YI, ON, and MY received lectureship fees; and HK received speaker fees from Nippon Shinyaku Co., Ltd. MY and OYo received advisory board fees; MT, MY, OYo, and NS received consultancy fees; YI and MG received grants; and YI, MT, MG, MY, OYo, and NS received lectureship fees from Ono Pharmaceutical Co., Ltd. MT received advisory board fees; YI, MT, and OYo received consultancy fees; YI and MG received grants; OYa, YI, MT, MG, OYo, and NS received lectureship fees; and HK received speaker fees from Pfizer Japan Inc. YI received grants from RaQualia. OYo received advisory board fees, consultancy fees, and lectureship fees from Sanwa Kagaku Kenkyusho Co., Ltd. MG, MY, and OYo received advisory board fees; OYa, MT, MG, MY, and OYo received consultancy fees; HK, YI, and MG received grants; YI, MT, MG, and OYo received lectureship fees; and HK received personal fees from Taiho Pharmaceutical Co., Ltd. HK received grants from Takeda Pharmaceutical Company Ltd.

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## Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

**Figure S1.** Change from baseline in mean pulse rate (measured by patients) (a) on awakening and (b) 6 h post-dose.
**Figure S2.** Change from baseline in mean SBP (measured by patients) (a) on awakening and (b) 6 h post-dose.
**Figure S3.** Change from baseline in mean DBP (measured by patients) (a) on awakening and (b) 6 h post-dose.
**Table S1.** Inclusion and exclusion criteria.
**Appendix S1.** MILAI II study group.

## Editorial Comment

# Editorial Comment to Long-term safety and efficacy of antimuscarinic add-on therapy in patients with overactive bladder who had a suboptimal response to mirabegron monotherapy: A multicenter, randomized study in Japan (MILAI II study)

β3-Adrenergics have been accepted as an alternative to antimuscarinics for overactive bladder (OAB) treatment. The efficacy of β3-adrenergics has been shown, and they are associated with a mechanism of action that differs from that of antimuscarinics. Using a combination of both drugs is a possible option for OAB treatment, and a randomized controlled trial has been reported.[1] However, the major study to date analyzed add-on therapy with the β3-adrenergic, mirabegron, in patients with OAB.[2] Furthermore, these earlier studies had a duration of 18 weeks, consisting of a 2-week screening period and a 16-week treatment period. Because OAB is a chronic condition, the long-term effects of a proposed treatment must be evaluated. From this perspective, the study by Yamaguchi *et al.* represents a well-designed clinical trial for adding on different antimuscarinic agents to an initial mirabegron treatment for patients with OAB.[3] Before this study, no randomized study was carried out to analyze the long-term safety and efficacy of antimuscarinic add-on therapy in patients receiving mirabegron. Furthermore, these authors selected four commonly used antimuscarinics for their analysis and incorporated a 52-week follow-up period in the current study setting, which has novelty in this field.

There were some potential limitations of this study. Oxybutynin and fesoterodine were not included in this study (darifenacin and trospium are not in use in Japan). Oxybutynin is not commonly prescribed in Japan. Fesoterodine, which is a prodrug of 5-hydroxymethyl tolterodine, is unaffected by the varying expression of hepatic enzymes, such as CYP2D6, and shows superior efficacy over tolterodine.[4] At week 8 of the current study, just 8.0% of patients required an increase in antimuscarinic dose, but the tolterodine dose could not be increased because of prescribing restrictions. If fesoterodine had been selected instead of tolterodine in this study, the problem of tolterodine dose escalation could have been avoided. Although this randomized controlled trial was not designed to assess whether one antimuscarinic is superior to another antimuscarinic with respect to add-on therapy, we are interested in this issue.

Our aging population is also relevant to this discussion, as symptoms of OAB increase with age, and almost one-third of adults aged ≥65 years have OAB symptoms.[5] In this study, the mean age of the patients was 65 years. In the near future, patients aged ≥75 years will be the main target of OAB management. Thus, we have considerable interest in an analysis focused on the safety and effectiveness of antimuscarinic add-on therapy in patients with OAB aged ≥75 years versus those who are aged <75 years.

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## Conflict of interest

None declared.

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