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ORIGINAL ARTICLE

# Solifenacin for overactive bladder: secondary analysis of data from VENUS based on baseline continence status

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**Abstract**
*Introduction and hypothesis* VENUS evaluated the efficacy of solifenacin on urgency in patients with overactive bladder (OAB). We hypothesized that solifenacin would be comparably efficacious in continent and incontinent patients.
*Methods* VENUS was a 12-week, placebo-controlled trial in patients with OAB. Treatment efficacy was assessed using bladder diaries and patient-reported outcome measures. The primary endpoint was the change in daily urgency episodes. Exploratory subgroup analyses were conducted using baseline continence status.
*Results* Solifenacin reduced urgency episodes versus placebo in continent (−3.4 vs. −2.3) and incontinent patients (−4.2 vs. −2.9) and incontinence episodes (−2.1 vs. −1.2) in that subgroup; 58% versus 42% of incontinent patients receiving solifenacin versus placebo were continent at study end. In both cohorts, solifenacin- versus placebo-treated patients showed greater improvements in perceptions of urgency severity, symptom bother, and health-related quality of life.
*Conclusion* This post hoc analysis demonstrates the efficacy of solifenacin regardless of baseline continence status.

**Keywords** Overactive bladder · Urgency · Symptom bother · Continence status · Subjective assessment

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## Introduction

Overactive bladder (OAB) is a prevalent, symptom-based condition characterized by urgency, with or without urgency urinary incontinence (UUI), usually with increased daytime frequency and nocturia [1, 2]. This definition, developed by the International Continence Society (ICS), identifies urgency—a sudden compelling desire to pass urine, which is difficult to defer—as the cardinal symptom of OAB, because it is thought to drive the other symptoms [3]. Moreover, the definition implies that the presence of urgency alone is sufficient for a diagnosis of OAB irrespective of the presence of other symptoms, particularly UUI.

Prevalence estimates from epidemiologic studies suggest that, in the general population of people who report having OAB, most do not have incontinence [4–6]. By contrast, in most OAB clinical trials, the majority of patients report incontinence at enrollment. In studies for which UUI is not an inclusion criterion, it may be that incontinent patients are more likely to seek treatment and/or be willing to participate in a clinical study. Regardless, effective treatments are available for most who have bothersome symptoms, and antimuscarinics, as first-line therapy for

OAB, have proven efficacy in reducing OAB symptoms, including UUI [7].

To date, few studies have investigated the efficacy of antimuscarinics in continent patient populations [8, 9] or compared the relative efficacy of these agents in continent versus incontinent patients [10, 11]. Moreover, none of the pivotal trials evaluated urgency as a primary efficacy endpoint, likely because the concept has been difficult to define and measure. Rather, a reduction in micturition frequency or UUI episodes was the primary outcome of interest. As a result of recent research, new objective and subjective measures of urgency have been validated, permitting a better understanding of the full impact of this symptom on patients with OAB, with or without UUI.

Solifenacin is an antimuscarinic approved for the treatment of OAB, and in all four phase III pivotal studies, the primary endpoint was the change in the number of micturitions per 24 hours [12–14]. VESIcare Efficacy and Safety in PatieNts with Urgency Study (VENUS) was the first OAB trial designed to evaluate urgency as the primary efficacy endpoint, and both objective and subjective measures were used [15, 16]. The large number of patients enrolled (739 randomized) enabled us to conduct a post hoc analysis of data stratified by patients' baseline continence status. We hypothesized that solifenacin would be comparably efficacious in continent and incontinent patients.

## Materials and methods

Complete details regarding the VENUS design and patient population have recently been published [15]. Briefly, VENUS was a multicenter, randomized, double-blind, placebo-controlled trial in which patients (aged ≥18 years) with OAB symptoms for ≥3 months received flexibly dosed solifenacin (5 or 10 mg) or placebo once daily for 12 weeks. The primary endpoint was the change in the mean number of urgency episodes per 24 h. All urgency episodes as well as other urinary events were recorded in bladder diaries that patients completed for 3 consecutive days at baseline and just before study visits at weeks 4, 8, and 12.

Secondary endpoints included other diary-based variables: frequency, incontinence episodes, nocturia, and warning time (assessed at baseline and week 12, using a stopwatch). Warning time is defined as the time from the first sensation of urgency to voiding and has been used as an endpoint to assess treatment efficacy on urgency [17]. Validated patient-reported outcome (PRO) and health-related quality of life (HRQL) measures included the Indevus Urgency Severity Scale (IUSS) [18], Urgency Perception Scale (UPS) [19], Patient Perception of Bladder Condition (PPBC) [20], and Overactive Bladder Questionnaire (OAB-q) [21].

Two of the four PRO measures used in VENUS have been validated to assess patient perception of urgency severity. On the single-item IUSS, patients rated the severity of urgency on a four-point scale: 0, None (no urgency); 1, Mild (awareness of urgency, but easily tolerated); 2, Moderate (enough urgency discomfort that it interferes with usual activity/tasks); and 3, Severe (extreme urgency discomfort that abruptly stops all activity/tasks) [18]. On the single-item UPS [19], patients are asked to describe their typical experience when they feel the desire to urinate. The three response options are: 1 ("I am usually not able to hold urine"), 2 ("I am usually able to hold urine until I reach the toilet if I go immediately"), and 3 ("I am usually able to finish what I am doing before going to the toilet"). Positive changes in UPS scores were coded as "Improved," no change was coded as "Unchanged," and negative changes were coded as "Worsened."

On the single-item PPBC [20], patients indicate which statement best describes the extent of their bladder-related problems. Responses range from 1 ("My bladder condition does not cause me any problems at all") to 6 ("My bladder condition causes me many severe problems").

The 33-item OAB-q comprises an eight-item Symptom Bother scale and a 25-item HRQL scale [21]. On the Symptom Bother scale, patients rate the level of bother associated with their OAB symptoms during the past 4 weeks on a six-point scale with responses ranging from 1 ("not at all") to 6 ("a very great deal"). The HRQL scale comprises four domains: Coping, Concern, Sleep, and Social Interaction. For each domain, patients indicate how often their OAB symptoms affected various activities during the past 4 weeks, with responses ranging from 1 ("none of the time") to 6 ("all of the time"). Item scores within each OAB-q scale and domain are summed and transformed to a 0-to-100 scale. Higher Symptom Bother scores indicate worse symptom bother, and higher HRQL scores indicate better HRQL.

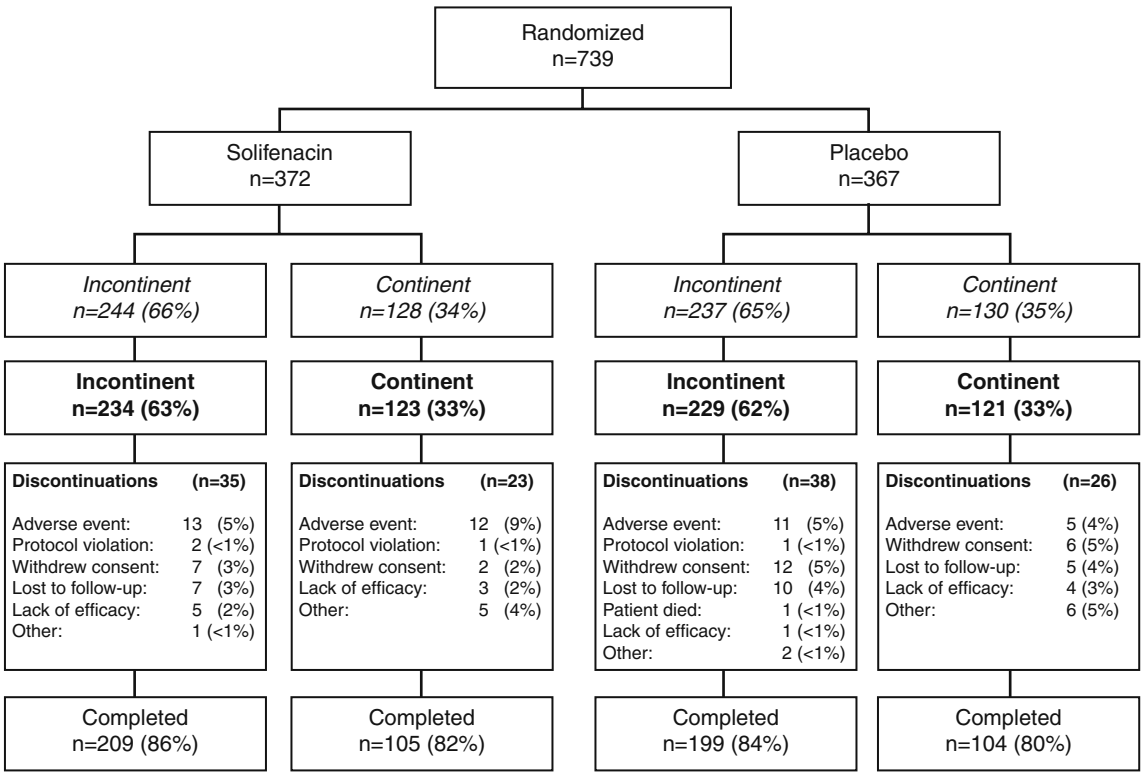
For this post hoc analysis, VENUS patient data were stratified by baseline continence status, which was originally assessed by study investigators using 3-day bladder diary data recorded before the baseline visit. If a patient recorded at least one incontinence episode during this period, s/he was classified as incontinent; likewise, if a patient did not record any episode of incontinence during this period, s/he was classified as continent. As with the primary analysis, the post hoc evaluation of efficacy used the full analysis set (FAS), which included all patients who received at least one dose of study medication, had baseline efficacy data, and had at least one corresponding post-baseline efficacy assessment. The safety analysis population included all patients who received at least one dose of study medication.

Owing to the post hoc nature of this analysis and the between-group differences in sample size of the subgroups, inferential statistical analyses were not performed. Instead, descriptive data that highlight numeric trends are presented to compare with results reported for the full VENUS population [15, 16] and to consider in the context of other studies reported in the literature. Moreover, the results are not presented separately by dose of solifenacin. As this was a flexible- and not fixed-dose study, the potential for self-selection bias would make the results of such comparisons difficult to interpret.

## Results

Of the 739 patients randomized (safety population), 707 comprised the FAS; 65% of patients reported incontinence at baseline and 35% did not (Fig. 1). Overall, women comprised the majority of patients enrolled in VENUS (84%), and nearly 70% reported incontinence at baseline. In contrast, about half (47%) of the male patients were incontinent at baseline. The proportion of patients who completed 12 weeks of treatment was similar across patient cohorts, and in all groups the most common reason for study discontinuation was an adverse event (Fig. 1). Baseline demographics were generally comparable between the cohorts, with few exceptions. As noted, a larger percentage of the incontinent cohort was female; incontinent patients were also about 3 years older and 7 kg heavier than continent patients (Table 1).

For the VENUS primary endpoint, both the continent and incontinent cohorts showed reductions in the mean number of urgency episodes after 12 weeks of solifenacin versus placebo (Fig. 2). The treatment differences in the continent and incontinent cohorts were −1.1 and −1.3, respectively. Micturition frequency in both continent and incontinent patients also decreased more among those taking solifenacin versus placebo (Fig. 2). Treatment differences were −0.5 and −0.9, respectively. Treatment-related changes in nocturia were small in both cohorts (Fig. 2). Patients in both continent and incontinent cohorts showed significant, within-group improvements in warning time from baseline (continent: solifenacin = 81.0 s, placebo = 74.0 s; incontinent: solifenacin 60.3 s, placebo = 55.0 s) to end of treatment (continent: solifenacin = 152.5 s, placebo = 85.0 s; incontinent: solifenacin = 102.8 s, placebo = 72.3 s). The treatment-group differences in the continent and incontinent cohorts were similar (16.0 and 22.2 s). In the incontinent cohort, patients who received solifenacin showed a mean decrease of −2.1 incontinence episodes per 24 h;




Entries in *italics* represent the safety population
Entries in **boldface** represent the full analysis set; 15 solifenacin and 17 placebo patients did not have post-baseline data

**Fig. 1** Patient disposition by baseline continence status (safety population)

**Table 1** Baseline demographic and clinical characteristics (FAS)

| | Incontinent | | Continent | |
|---|---|---|---|---|
| Characteristic/variable | SOL (*n*=234) | PBO (*n*=229) | SOL (*n*=123) | PBO (*n*=121) |
| Women, *n* (%) | 211 (90) | 198 (87) | 93 (76) | 93 (77) |
| Age, mean±SD | 59±13 | 59±15 | 56±15 | 56±15 |
| Weight, kg, mean±SD | 85.1±24.2 | 83.6±20.5 | 78.5±17.0 | 76.5±18.0 |
| Diary variables/24 h, mean±SD | (*n*=229) | (*n*=224) | (*n*=119) | (*n*=112) |
| Urgency episodes | 6.6±3.9 | 6.6±3.9 | 5.4±4.0 | 4.9±3.6 |
| Incontinence episodes | 2.8±2.7 | 2.6±2.7 | NA | NA |
| Micturition frequency | 11.7±3.9 | 11.6±3.5 | 11.6±3.4 | 11.9±3.8 |
| Nocturia episodes | 1.7±1.2 | 1.6±1.1 | 1.7±1.1 | 1.6±1.1 |
| Warning time, s, Median | (*n*=186) | (*n*=178) | (*n*=94) | (*n*=94) |
| | 60.3 | 55.0 | 81.0 | 74.0 |
| IUSS rating category, *n* (%) | (*n*=221) | (*n*=208) | (*n*=111) | (*n*=115) |
| 0 (None) | 0 (0) | 1 (<1) | 1 (<1) | 0 (0) |
| 1 (Mild) | 22 (10) | 31 (15) | 22 (20) | 32 (28) |
| 2 (Moderate) | 149 (67) | 126 (61) | 76 (69) | 73 (64) |
| 3 (Severe) | 50 (23) | 50 (24) | 12 (11) | 10 (9) |
| IUSS score, mean±SD | 2.1±0.6 | 2.1±0.6 | 1.9±0.6 | 1.8±0.6 |
| UPS rating category, *n* (%) | (*n*=221) | (*n*=208) | (*n*=111) | (*n*=115) |
| 1 (Cannot hold urine) | 45 (20) | 48 (23) | 5 (5) | 1 (<1) |
| 2 (Can hold urine briefly) | 162 (73) | 147 (71) | 81 (73) | 74 (64) |
| 3 (Can finish activity/task) | 14 (6) | 13 (6) | 25 (23) | 40 (35) |
| UPS score, mean±SD | 1.9±0.5 | 1.8±0.5 | 2.2±0.5 | 2.3±0.5 |
| PPBC score, Mean±SD | (*n*=222) | (*n*=208) | (*n*=111) | (*n*=116) |
| | 4.0±1.0 | 4.0±0.9 | 3.6±1.1 | 3.6±0.9 |
| OAB-q score, mean±SD | (*n*=222) | (*n*=208) | (*n*=110) | (*n*=116) |
| Symptom bother | 57.1±18.1 | 55.7±19.7 | 43.0±16.5 | 44.0±16.5 |
| HRQL total | 58.3±21.6 | 56.6±23.1 | 64.6±20.0 | 67.4±18.0 |
| Coping | 54.7±26.1 | 51.4±26.5 | 58.8±25.5 | 63.8±23.5 |
| Concern | 50.7±24.4 | 50.2±26.3 | 62.0±23.8 | 64.2±21.9 |
| Sleep | 53.8±26.6 | 52.8±28.0 | 56.3±25.1 | 56.7±26.5 |
| Social interaction | 79.4±23.4 | 77.6±25.2 | 85.8±19.2 | 88.4±15.5 |

*FAS* full analysis set, *SOL* solifenacin, *PBO* placebo, *SD* standard deviation, *IUSS* Indevus Urgency Severity Scale, *UPS* Urgency Perception Scale, *PPBC* Patient Perception of Bladder Condition, *OAB-q* Overactive Bladder Questionnaire, *HRQL* health-related quality of life

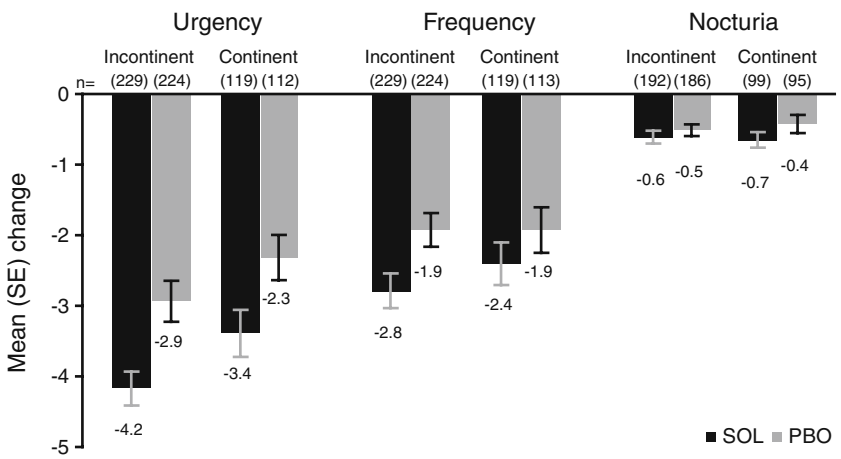



**Fig. 2** Mean (SE) changes from baseline to study end in 24-h urgency, frequency, and nocturia episodes by treatment group and baseline continence status. *SE* standard error, *SOL* solifenacin, *PBO* placebo

those who received placebo showed a mean decrease of −1.2 episodes per 24 h. As previously reported, among patients with incontinence at baseline, 58% of solifenacin- and 42% of placebo-treated patients reported no incontinence episodes at study end [15].

For the subjective assessment of urgency, mean score changes from baseline to study end on the IUSS were larger in the solifenacin versus placebo groups for both incontinent (−1.0 vs. −0.6) and continent patients (−0.7 vs. −0.4), suggesting an improvement in urgency severity regardless of continence status. Likewise, mean score changes on the UPS were larger in the solifenacin versus placebo groups for incontinent (+0.5 vs. +0.3) and continent patients (+0.3 vs. +0.1). In this case, positive score changes indicate reduced urgency severity. Categorically, more solifenacin- versus placebo-treated patients in the incontinent and continent cohorts showed improvement (≥1-point change) on the IUSS and UPS by study end (Fig. 3a,b).

On the PPBC at baseline, incontinent patients rated the extent of their bladder problems as more serious (mean score, 4.0) than did continent patients (mean score, 3.6). After 12 weeks of solifenacin, the percentages of patients who showed at least a one-point improvement in score were comparable between the continent (63%) and incontinent cohorts (67%). After 12 weeks of placebo, 48% of continent and incontinent patients showed at least a one-point improvement on the PPBC. By the end of treatment, more solifenacin than placebo patients shifted toward lower scores representing fewer bladder-related problems, and this was evident in both the incontinent and continent cohorts (Fig. 4a,b).

At baseline, incontinent patients reported perceiving greater OAB-associated symptom bother and impact on HRQL than did continent patients, with higher OAB-q scores on all scales and domains (range of differences: 3.2–12.9). In particular, incontinent patients reported more bother and concern due to their symptoms (Table 1). After 12 weeks, all changes on the OAB-q were greater after solifenacin than placebo (Table 2) in both the incontinent and continent groups.

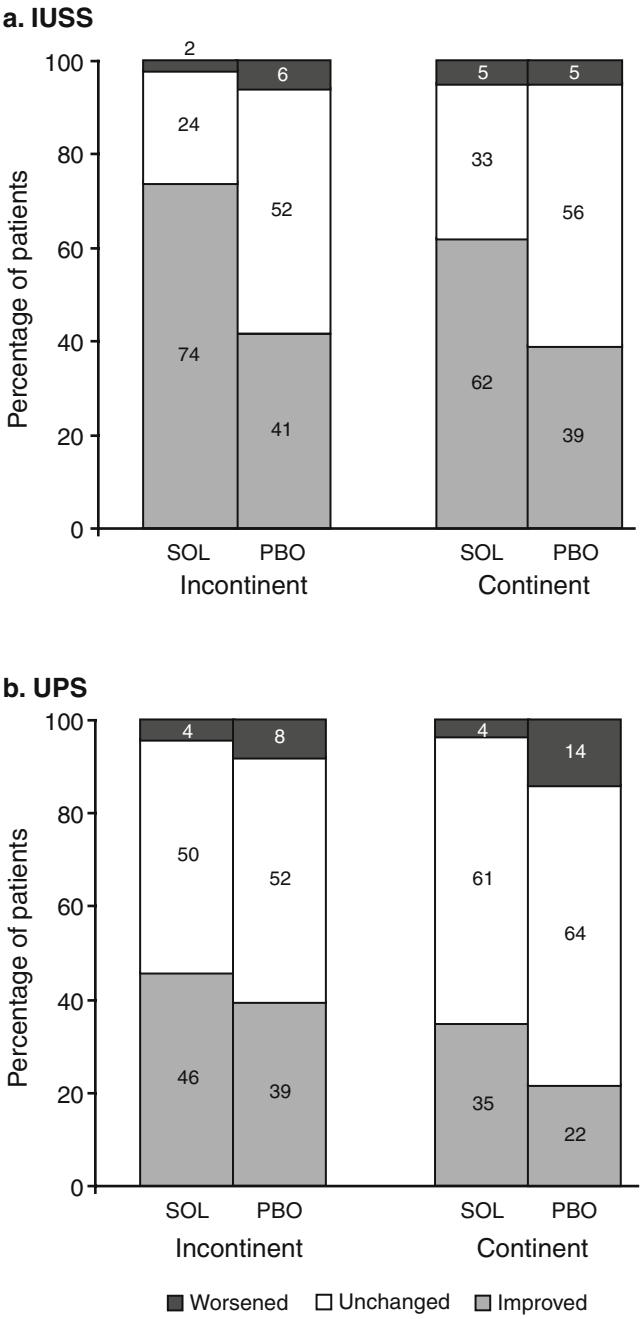



**Fig. 3** Distribution of patients at study end that was Improved (at least one-point negative change), Unchanged (zero), or Worsened (at least one-point positive change) on the IUSS (**a**) and Improved (at least one-point positive change), Unchanged (zero), or Worsened (at least one-point positive change) on the UPS (**b**) by treatment group and baseline continent status. *IUSS* Indevus Urgency Severity Scale, *SOL* solifenacin, *PBO* placebo, *UPS* Urgency Perception Scale

## Discussion

VENUS was the first large, placebo-controlled, OAB trial to assess ICS-defined urgency as the primary efficacy outcome using both diary- and PRO-based data. The use of both types of measures provides the opportunity to understand patients' global experience with OAB, including their own assessment of symptom severity, symptom-specific bother, effects on HRQL, and the extent of their bladder-related problems.

We conducted this post hoc analysis of VENUS to explore the efficacy of solifenacin on urgency and other urinary events in patients who were continent or incontinent at baseline. VENUS was ideal for this investigation for two reasons: urgency was prespecified

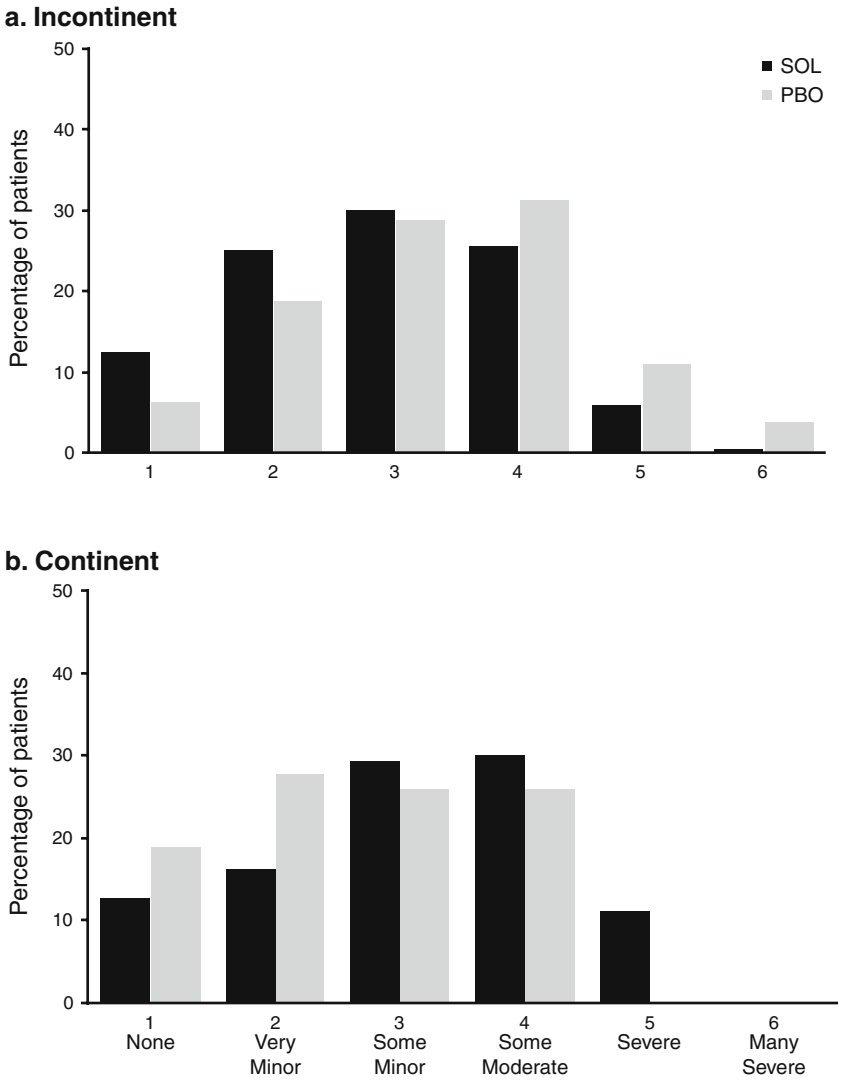



**Fig. 4** End-of-study distribution of patients by PPBC rating among incontinent (**a**) and continent (**b**) patients by treatment group. *PPBC* patient perception of bladder condition, *SOL* solifenacin, *PBO* placebo

as the primary efficacy outcome, and sufficient numbers of patients were enrolled in both subgroups. As in other OAB clinical trials, the majority of VENUS patients (65%) were incontinent at baseline.

Inherent limitations of a post hoc analysis notwithstanding, both continent and incontinent patients showed treatment-related improvements in urgency and other endpoints consistent with the statistically significant results

**Table 2** OAB-q: Mean changes from baseline to study end by baseline continence status

| | Incontinent | | | Continent | | |
|---|---|---|---|---|---|---|
| OAB-q scale/domain | SOL ($n$=221) | PBO ($n$=208) | Difference | SOL ($n$=110) | PBO ($n$=116) | Difference |
| Symptom bother[a] | –31.1 | –20.8 | −10.3 | –21.7 | –14.4 | −7.3 |
| HRQL total[b] | 23.9 | 19.5 | 4.4 | 20.0 | 13.1 | 6.9 |
| Coping | 25.6 | 21.2 | 4.4 | 23.5 | 16.1 | 7.4 |
| Concern | 30.5 | 22.9 | 7.6 | 24.1 | 15.7 | 8.4 |
| Sleep | 22.5 | 19.4 | 3.1 | 21.5 | 12.2 | 9.3 |
| Social interaction | 12.9 | 12.0 | 0.9 | 7.1 | 5.7 | 1.4 |

*OAB-q* Overactive Bladder Questionnaire, *SOL* solifenacin, *PBO* placebo, *HRQL* health-related quality of life

[a] Negative value indicates improvement

[b] Positive value indicates improvement

reported for the VENUS primary analysis [15]. In VENUS, mean changes in 24-h urgency episodes, micturition frequency, and incontinence episodes were significantly reduced after solifenacin versus placebo ($p<0.01$). In the current analysis, there were greater and more consistent reductions in urgency, micturition frequency, and warning time among both continent and incontinent patients after solifenacin versus placebo.

These findings are consistent with published results from other solifenacin studies. In a pooled analysis of four randomized, placebo-controlled, fixed-dose, Phase III trials [8], patients who were continent at baseline experienced mean changes in urgency episodes and micturition frequency of −3.2 (5- and 10-mg groups) and −2.6 (5 mg) and −2.8 (10 mg), respectively, after 12 weeks of solifenacin. In the current analysis, similar trends emerged, with daily reductions of −3.4 for urgency and −2.4 for frequency. The corresponding reductions among incontinent patients were −4.2 and −2.8, respectively.

Among incontinent patients taking solifenacin in VENUS, 58% became continent by week 12 (the placebo rate was 42%) [15], a result consistent with continence rates of ≥50% reported in a pooled analysis of solifenacin studies [22]. In both cohorts, warning time increased about 30 s after solifenacin and <15 s after placebo. The increase in warning time may be related to the reductions in incontinence episodes; having more time may enable a patient to reach the toilet before an episode of incontinence. However, given that the solifenacin-related improvements in urgency episodes and warning time were comparable between continent and incontinent patients, it is likely that at least one additional factor contributed to the significant reductions in incontinence episodes after solifenacin versus placebo observed in this subgroup [15].

VENUS included multiple subjective assessment tools to evaluate the patients' perspectives with regard to the nature of their symptoms, the impact of these symptoms on their daily lives, and importantly, their perception of the effects of treatment. The findings showed that the numeric changes in scores on the IUSS, UPS, PPBC, and OAB-q were significant for solifenacin over placebo, which is consistent with the primary analysis [15, 16]. For most endpoints, treatment differences trended toward favoring the incontinent cohort, with the exception of the OAB-q HRQL domains, which all favored the continent cohort. While it may be difficult to translate small numeric changes in scores to clinically relevant findings, categorical improvements on the IUSS, UPS, and PPBC may be easier to interpret in this regard. On the IUSS, UPS, and PPBC, more solifenacin than placebo patients showed at least a one-point improvement and a shift toward less severe urgency and fewer bladder-related problems.

In VENUS, patients who received 12 weeks of placebo also showed reductions in urgency and increases in warning time. This is not unusual, as most OAB studies have shown a measurable placebo response, which can be attributed to a number of factors, including increased personal attention received as a study participant, learning more about OAB and its treatment, and the training effect associated with maintaining a bladder diary [23]. Nevertheless, the results with active drug were superior to placebo, demonstrating the therapeutic efficacy of solifenacin.

Although solifenacin is the first antimuscarinic to significantly and statistically increase warning time at an approved dose compared with placebo, it is important to note that this measure is only relevant in patients with urgency. It is not possible to measure warning time in patients who no longer have urgency symptoms after treatment for OAB with any antimuscarinic.

Although VENUS included both continent and incontinent patients, the study was not designed or powered to detect a treatment difference among patients in these subgroups. Nevertheless, sufficient numbers of patients were available to describe numeric trends in these cohorts for hypothesis generation. To this end, these findings may be useful when considered in the context of the few existing reports in the literature and to inform future clinical trials. For example, in this analysis, incontinent patients were, on average, older and heavier than continent patients, and a higher percentage of incontinent patients were women. Demographic differences may offer valuable insights into how patient profiles might influence treatment outcomes. Characterizing the OAB patient population in this way can help identify potential risk factors and identify additional variables that might be incorporated into future studies.

VENUS demonstrated statistically significant improvements for both diary- and PRO-based endpoints in patients receiving solifenacin versus placebo [15, 16]. This post hoc evaluation is one of the few reports to explore the extent of treatment-related improvements in the subgroups of patients with or without incontinence at baseline. Our findings confirm and extend the current body of evidence and show that patients derived treatment benefits from solifenacin regardless of continence status. These benefits were manifested by reductions in OAB symptoms and by changes in the patients' perception of symptom severity, symptom-specific bother, impact on HRQL, and the overall perception of their bladder-related problems.

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**Conflicts of interest** Dr. Toglia is a consultant and speaker for Astellas; Dr. Ostergard is a consultant and speaker for Astellas, GlaxoSmithKline, Novartis, Pfizer and Watson. Dr. Fakhoury is an employee of Astellas. Mr. Andoh and Dr. Hussain were employees of Astellas at the time the study was conducted and have no other conflicts of interest to disclose.

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