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Bladder Wall Thickness in Women With Symptoms of Overactive Bladder and Detrusor Overactivity: Results From the Randomised, Placebo-Controlled Shrink Study

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Aims: Measurement of bladder wall thickness (BWT) by transvaginal ultrasound (TVUS) may be a less invasive method to diagnose overactive bladder (OAB) or detrusor overactivity (DO) and monitor response to therapy. This study assessed whether treatment with solifenacin affects BWT. **Methods:** This was a double-blind, randomised, placebo-controlled, phase 4 study. Adult women with OAB symptoms received solifenacin 5 or 10 mg or placebo once daily for 12 weeks. The co-primary endpoints were change from baseline to Week 12 in TVUS-measured BWT and urinary nerve growth factor. Only results for BWT are presented here. **Results:** Overall, 547 patients were randomised, 501 patients had a baseline BWT measurement, and change from baseline could be calculated for 478 patients. Mean BWT at baseline was 5.08 mm (range 2.2–11.1, SD = 1.14) and was normally distributed. A significant reduction in BWT from baseline to 12 weeks versus placebo was observed with solifenacin 5 mg (−0.42 vs. −0.16 mm, $P = 0.03$), but not with the 10 mg dose or with pooled solifenacin, considered the primary comparison. Both solifenacin doses were associated with improvements in efficacy and patient satisfaction endpoints versus placebo. Solifenacin was well tolerated, with dry mouth being the most common adverse event. **Conclusions:** There was no consistent effect of solifenacin on BWT in women with OAB/DO, despite improvements in efficacy endpoints. This study suggests that routine clinical assessment of BWT with TVUS for monitoring the effects of OAB/DO treatment is not clinically useful. *Neurourol. Urodynam. 35:819–825, 2016.*
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INTRODUCTION

Overactive bladder (OAB) is a common symptom syndrome affecting ~13% of adult women.[1] It is a symptomatic diagnosis, defined by the International Urogynaecological Association and the International Continence Society as urinary urgency, usually accompanied by daytime frequency, and nocturia, with or without urgency urinary incontinence, in the absence of a urinary tract infection or other obvious pathology.[2] Antimuscarinics, the principal form of pharmacotherapy for OAB in both sexes,[3,4] are thought to exert their activity in part via detrusor muscle contraction suppression. Detrusor overactivity (DO), defined by involuntary detrusor contractions during the bladder filling phase, may be spontaneous or provoked.[2] Although associated with OAB, DO must be diagnosed using conventional urodynamics; however such tests are expensive, time-consuming, invasive, and carry risks such as urinary tract infection.[5] Thus, there is a need for a less invasive test for the objective diagnosis of DO.

Increased bladder wall thickness (BWT) is believed to be associated with DO, based on observations in animal studies, in which repetitive involuntary contractions of the detrusor caused by artificial bladder outlet obstruction result in bladder wall hypertrophy,[6] and was confirmed in studies in men with bladder outlet obstruction.[7,8] Previous studies have shown that BWT (as visualised by ultrasound) is greater in women with OAB or DO than in women with stress urinary incontinence or normal urinary function,[9–12] highlighting BWT's potential as a biomarker for OAB or DO diagnosis in women.[13] In addition, antimuscarinic treatment has been associated with decreases in BWT,[14–16] suggesting that BWT might also be useful as a measure of therapeutic response, potentaily providing insights into the mechanism of action of antimuscarinics.

The SHRINK study assessed whether different doses of solifenacin, an antimuscarinic, affect BWT, and additionally, whether BWT can be used to assess antimuscarinic therapy effectiveness in the treatment of women with OAB and DO. The rationale for this approach is that if BWT does not respond to effective OAB/DO treatment, it is also unlikely to be useful as a diagnostic biomarker.

PATIENTS AND METHODS

Study Design

This phase 4, multicentre study (NCT01093534) comprised a 2-week, single-blind, placebo run-in period followed by a 12-week, double-blind, randomised, placebo-controlled, parallel-group treatment period. The study investigated the effects of solifenacin (Astellas Pharma, Chertsey, UK) on BWT, uNGF, and urinary brain-derived neurotrophic factor (uBDNF) in female patients with OAB and a urodynamic diagnosis of DO. Eligible patients were randomised 1:1:1 using a centrally controlled interactive response technologies system (Cenduit GmbH, Allschwil, Switzerland) to receive solifenacin 5 mg, 10 mg, or placebo once daily for 12 weeks. Solifenacin and corresponding placebo tablets were indistinguishable. The study was conducted at 79 centres in 20 countries across Europe, the Middle East, and North America from January 2010 to June 2011, in accordance with the International Conference on Harmonisation—Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All study materials were reviewed and approved by local Independent Ethics Committees, and all patients provided written informed consent before screening.

Patients

Women aged ≥ 18 years with OAB, including urinary urgency, frequency, and/or urgency incontinence, for at least 3 months, and a urodynamic diagnosis of DO within 1 year were eligible for enrolment. Inclusion was independent of number or amplitude of involuntary detrusor contractions. No antimuscarinic therapy within 6 months or botulinum toxin therapy within 9 months prior to the screening visit was permitted and patients were required to have a post-void residual (PVR) volume of <50 ml. Key exclusion criteria were: evidence of urinary tract infection, bladder outlet obstruction, or urogenital prolapse (greater than grade II); history or diagnosis of specific urinary conditions, including urinary retention, stress urinary incontinence, or neurogenic DO; known hypersensitivity to study medications or their excipients; or any other clinical condition, diagnosis, symptomatology, or ongoing investigation that in the opinion of the investigator, contraindicated their participation.

Study Assessments

The co-primary endpoints were changes from baseline to Week 12 in transvaginal ultrasound (TVUS)-measured BWT and urinary nerve growth factor (uNGF) level, normalised by urine creatinine. Secondary endpoints included associations between BWT and baseline parameters, and change in BWT and change in efficacy endpoints; change in uBDNF, associations between uNGF and OAB symptoms at baseline, changes in micturition diary variables, the Overactive Bladder Questionnaire (OAB-q) with health-related quality of life (HRQoL) total score and subscores, including the symptom bother score,[17,18] Urgency Bother-Visual Analogue Scale (UB-VAS),[19] Treatment

Satisfaction-Visual Analogue Scale (TS-VAS)[20] and Patient Perception of Bladder Condition (PPBC).[17,18] Adverse events were reported throughout the study. Endpoints relating to change in uNGF and uBDNF, micturition diary variables, and patient reported outcomes will be reported separately.

TVUS Measurement of BWT

BWT was measured with a near-empty bladder (PVR volume <50 ml) by assessment of TVUS images at three measurement locations of the bladder wall (anterior wall, dome, and trigone, reviewed by Oelke et al. 2013[13]) by two central "blinded" readers, and a mean BWT was derived per patient at each visit. A third "blinded" adjudicator was used in cases of significant variability ($P < 0.05$) between the image mean values of the two main central readers, defined as differences greater than Bland–Altman limits of agreement (mean difference $\pm 1.96^*$SD of differences),[21] or when one reader provided a measurement for only one location. If both central readers provided numerical assessments for no more than one location, the image quality was considered low, and the image was excluded from further analyses. Following these central reader assessments, mean BWT values per patient and visit were calculated as least-square (LS) mean values with an ANOVA model (fixed effects for central readers [3 readers] and bladder wall location) to correct for a potential reader bias by having some images assessed in addition by a third central reader.

Statistical Analyses

The study was designed to have a power of at least 80% for detecting a treatment difference of 0.5 mm between pooled solifenacin and placebo (the primary treatment comparison) in mean change in BWT from baseline to end of study, assuming a standard deviation of 1.65 mm. An alpha of 0.025 (Bonferroni adjustment) was used in the sample size calculation to adjust for the overall type I error rate for defining two co-primary endpoints (BWT and uNGF). Exploratory comparisons between single treatment arms ($\alpha = 0.05$) had a power of 76% to detect a statistical significant difference, if the real treatment difference was at least 0.5 mm. Assuming that 12% of patients might drop out early or have no valid BWT measurements, 537 patients were to be randomised to achieve 471 patients (157 in each of the three treatment arms) for whom change from baseline in BWT could be calculated.

BWT analyses were carried out in the BWT full analysis set (FAS-BWT), defined as all randomised patients who received at least one dose of study medication and had a BWT measurement at baseline. Safety analyses were carried out in the safety population, which comprised all randomised patients who received at least one dose of randomised study medication and for whom any data were reported after the first dose of study drug.

The pre-planned primary analysis used an ANCOVA model with treatment (three arms) and geographical region as fixed factors, and baseline BWT as a covariate. Treatment comparisons were estimated as two-sided contrast with 95% confidence interval (CI). The significance level for the primary treatment comparison was adjusted for the two co-primary variables using the stepwise Hochberg procedure for controlling the overall risk of type 1 error. A significance level of $P = 0.05$ was used for exploratory treatment comparisons between each treatment arm. Non-parametric Wilcoxon rank-sum test were performed as secondary tests for comparing treatment arms without requiring model assumptions. Treatment by baseline interaction was graphically explored (scatter plot with regression line within each treatment arm)

and by adding the interaction term to the ANCOVA model in a separate analysis.

A post hoc BWT analysis (descriptive statistics and Wilcoxon rank-sum test) stratified by BWT at baseline ($\leq$5 mm or >5 mm) was carried out. This analysis was performed because a BWT $\leq$5 mm is considered normal by some authors, and to allow comparison of the results of the present study with data from a previous study[14] that included only patients with baseline BWT >5 mm. This post hoc analysis also illustrates the phenomenon known as "regression to the mean," which can be observed for any random variable or one whose measurement is subject to error. A variable that is extremely large or small on its first measurement will tend to be closer to the average on its second measurement, whereas if it is extreme on its second measurement, it will tend to have been closer to the average on its first measurement.

Pearson correlation coefficients (for continuous scales) (r_P) and Spearman rank correlation coefficients (for categorical or mixed scales) (r_S) were calculated to explore the relationships between baseline characteristics and mean BWT at baseline, as well as between changes in efficacy variables and mean BWT from baseline to Week 12. Missing values at Week 12 were imputed using the last observation (Week 6 or End of Study) carried forward (LOCF), except for the correlation analyses.

RESULTS

Patients and Baseline Characteristics

Of 673 women screened, 547 were randomised, and 543 received at least one dose of trial medication and were included in the safety analysis set; 501 patients had baseline BWT readings and were included in the FAS-BWT (Fig. 1). Change from baseline in BWT could be calculated for 478 patients. Thirty-five patients (6.4%) discontinued prematurely, primarily owing to withdrawal of consent (14, 2.6%), adverse events (9, 1.6%), lack of efficacy (4, 0.7%), or other reasons (8, 1.5%). No patients deviated from the protocol (0%) or were lost to follow-up (0%). Baseline characteristics are summarised in Table I: mean age was 54.9 years, most (95.6%) of the patients were Caucasian, and 99.4% had a confirmed diagnosis of DO. Patients had an average duration of OAB of 3.8 years and 54.5% had OAB with incontinence; however, only 9% had received previous treatment for OAB, most commonly antimuscarinics (e.g., solifenacin 2.8%, tolterodine 1.3%). Five patients in the placebo group, one patient in the solifenacin 5 mg group and three patients in the solifenacin 10 mg group had received a non-pharmacological OAB treatment before the start of the study.

Change in BWT

Mean BWT at baseline was 5.08 mm (range 2.2–11.1 mm) and followed a normal distribution (SD 1.14 mm) (Fig. 2). Overall, BWT was decreased from baseline to Week 12 (last observation carried forward, LOCF) with solifenacin 5 mg (LS mean $-$0.42 mm) compared with placebo ($-$0.16 mm; $P = 0.03$) (Table II, Fig. 3A); however, there were no significant differences between the solifenacin 10 mg or pooled solifenacin groups and placebo ($P = 0.477$ and $P = 0.095$) (Table II). The difference between solifenacin 5 mg and 10 mg was not statistically significant.
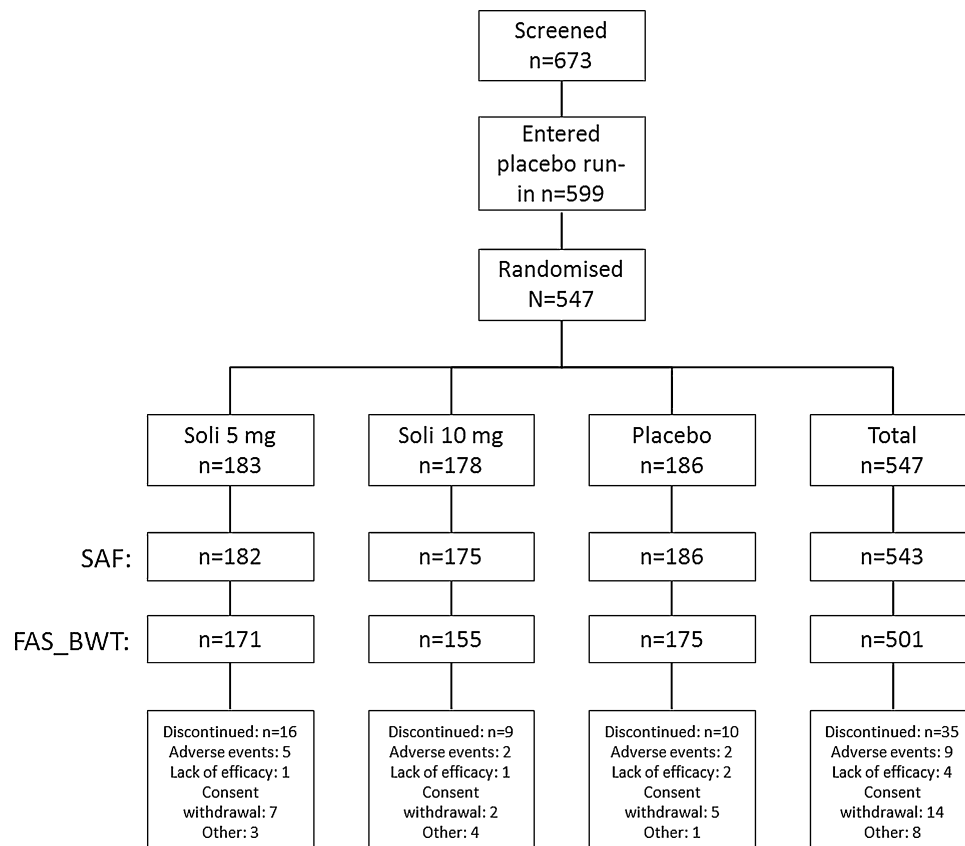
Figure 1. Patient flow. BWT, bladder wall thickness; FAS, full analysis set; SAF, safety population; Soli, solifenacin.

TABLE I. Baseline Characteristics (Safety Population)

	Placebo (n = 186)	Solifenacin 5 mg (n = 182)	Solifenacin 10 mg (n = 175)	Total (n = 543)
Mean age, years (SD)	53.7 (13.0)	55.5 (13.0)	55.5 (13.3)	54.9 (13.1)
Race, n (%)				
White	177 (95.2)	177 (97.3)	165 (94.3)	519 (95.6)
Black	1 (0.5)	1 (0.5)	2 (1.1)	4 (0.7)
Asian	4 (2.2)	1 (0.5)	2 (1.1)	7 (1.3)
Other	4 (2.2)	3 (1.6)	6 (3.4)	13 (2.4)
Mean BMI, kg/m^2 (SD)	27.5 (5.5)	28.4 (5.7)	27.9 (5.4)	27.9 (5.5)
DO diagnosis, n (%)	186 (100.0)	180 (98.9)	174 (99.4)	540 (99.4)
Previous OAB treatment, n (%)	19 (10.2)	17 (9.3)	13 (7.4)	49 (9.0)
Mean duration of OAB, months (SD)	49.6 (83.6)	43.3 (60.6)	43.3 (66.4)	45.4 (71.0)
Type of OAB, n (%)				
With incontinence	101 (54.3)	95 (52.2)	100 (57.1)	296 (54.5)
Without incontinence	85 (45.7)	87 (47.8)	75 (42.9)	247 (45.5)

BMI, body mass index; DO, detrusor overactivity; OAB, overactive bladder; SD, standard deviation.

The effect of the baseline covariate in the ANCOVA model was highly significant ($P < 0.0001$) and treatment comparisons are adjusted for mean baseline BWT observed in the total population. Analysis of residuals and the test for treatment by baseline interaction did not lead to concerns regarding the appropriateness of the ANCOVA model; however, since a large proportion of subjects with low BWT at baseline showed increased BWT when measured at the end of treatment a high variation and a systematic pattern that could be described as regression to the mean due to measurement variability were observed on a scatterplot (Fig. 3B).

A post hoc analysis of subgroups defined by baseline BWT (≤ 5 mm, > 5 mm, Table II, Fig. 3C), showed increases in mean (SD) BWT from baseline to Week 12 for solifenacin 5 mg, 10 mg, and placebo of 0.25 (1.06), 0.30 (0.92), and 0.43 (1.10) mm, respectively, in patients with baseline BWT ≤ 5 mm and decreases of 0.59 (1.43), 0.55 (1.23), and 0.51 (1.26) mm, respectively, in patients with baseline BWT > 5 mm. However, no treatment comparisons versus placebo performed with Wilcoxon rank-sum tests were statistically significant (Table II). The observation that the treatment group mean values increased across all three treatment arms in subjects with baseline ≤ 5 mm and decreased in subjects with baseline BWT > 5 mm is an example of the phenomenon known as "regression to the mean," which can be observed for any random variable or a variable with some measurement variation.

Change in Secondary Efficacy Endpoints

Significant improvements in OAB-q symptom bother, UB-VAS, TS-VAS, and PPBC score versus placebo were observed in patients receiving either solifenacin 5 or 10 mg. Urgency micturitions/24 h and incontinence episodes were significantly improved versus placebo with the 5 mg dose only, and micturitions/24 h with the 10 mg dose only. However, the study was not sufficiently powered for treatment comparisons in efficacy variables. These data are described in more detail in a separate article.

Analysis of Associations

Low but statistically significant correlations between mean BWT and age ($r_S = 0.094$, $P = 0.036$), parity ($r_S = 0.108$, $P = 0.016$), body weight ($r_P = 0.175$, $P < 0.001$), PPBC ($r_S = 0.094$, $P = 0.036$) and symptom bother as derived from the baseline OAB-q ($r_P = 0.128$, $P = 0.004$) were observed. There were no significant correlations with previous OAB treatment, type of OAB (wet vs. dry at baseline) or micturition diary variables at baseline (mean number of micturition events or urgency events). Correlations between the change from baseline to the end of treatment in BWT and secondary efficacy variables (micturition diary variables and patient-reported outcomes) were small and not statistically significant. This was the case for all arms, including placebo.
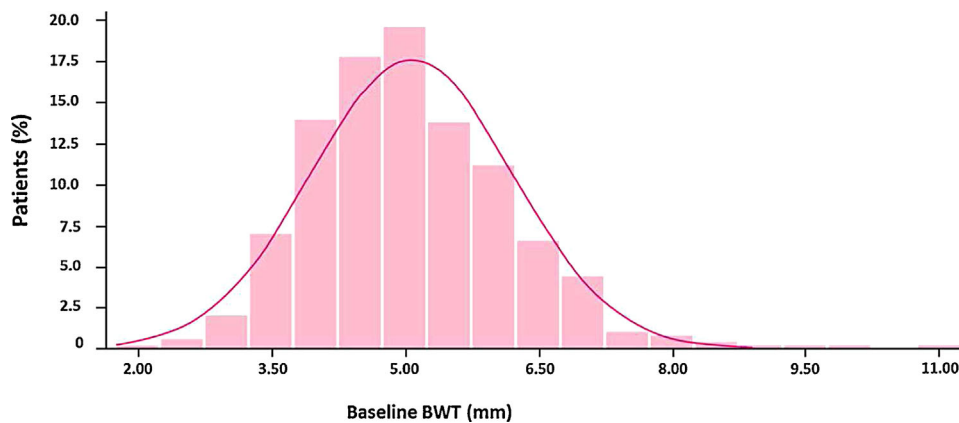

Figure 2. Distribution of BWT at baseline. In total, 501 patients had a baseline BWT image with a quality readable by at least two of the three central readers. Mean (SD) = 5.08 (1.14) mm.

TABLE II. Mean Change From Baseline to Week 12 (LOCF) in BWT (FAS-BWT)

	Placebo (n = 175)	Solifenacin 5 mg (n = 171)	Solifenacin 10 mg (n = 155)	Pooled Solifenacin (n = 326)
BWT (mm)				
Baseline (n = 501), mean (SD)	5.00 (1.08)	5.07 (1.19)	5.16 (1.15)	5.11 (1.17)
CFB to week 12 LOCF (n = 478)				
n	168	160	150	310
Mean (SD)	0.00 (1.26)	−0.29 (1.37)	−0.18 (1.18)	−0.24 (1.28)
P-value*, secondary test	—	0.055	0.269	0.077
LS mean CFB to week 12 LOCF	-0.162	−0.416	−0.246	—
Difference to Placebo	—	−0.254	−0.084	−0.169
95%CI	—	(−0.484; −0.025)	(−0.318; 0.149)	(−0.368; 0.030)
P-value, primary test	—	0.030	0.477	0.095
BWT baseline ≤5 mm				
Baseline				
n	96	89	68	157
Mean (SD)	4.22 (0.52)	4.22 (0.54)	4.18 (0.58	4.20 (0.56)
Week 12 LOCF				
n	91	82	66	148
Mean (SD)	4.65 (1.06)	4.48 (1.12)	4.47 (0.91)	4.47 (1.03)
P-value*, secondary test	—	0.167	0.551	0.230
BWT baseline >5 mm				
Baseline				
n	79	82	87	169
Mean (SD)	5.95 (0.78)	5.99 (0.99)	5.93 (0.85)	5.96 (0.92)
Week 12 LOCF				
n	77	78	84	162
Mean (SD)	5.42 (1.06)	5.14 (1.15)	5.40 (1.12)	5.27 (1.13)
P-value*, secondary test	—	0.198	0.800	0.383

*Wilcoxon rank-sum test. LS mean = Least Square Mean from ANCOVA. ANCOVA model included treatment and geographic region as fixed effects and baseline as covariate. BWT, bladder wall thickness; FAS, full analysis set; LOCF, last observation carried forward; SD, standard deviation.

Safety Endpoints

Overall, 151 patients (27.8%) reported at least one treatment-emergent adverse event (TEAE) during the double-blind treatment period: 41 (22.5%) with solifenacin 5 mg, 57 (32.6%) with solifenacin 10 mg and 53 (28.5%) with placebo. The most common TEAEs were dry mouth (12.9% for solifenacin vs. 1.1% for placebo) and constipation (4.8% for solifenacin vs. 3.8% for placebo).

DISCUSSION

A recent review of existing studies suggests that the reduction in BWT is a potentially useful biomarker for documenting success in patients with OAB and DO treated with antimuscarinics.[13] The SHRINK study assessed whether solifenacin treatment results in BWT changes and whether BWT is potential a biomarker for the assessment of antimuscarinic therapy effectiveness in the treatment OAB in women. Here, baseline BWT measurements showed a normal distribution with mean (SD) 5.08 (1.14) mm, meaning that only about 50% of women with DO and OAB included in the study had a baseline BWT value above 5.0 mm, a margin considered by some authors as an indication of increased BWT compared to healthy subjects.

The primary efficacy comparison of pooled solifenacin versus placebo showed no significant change in BWT after 12 weeks of treatment. Although mean BWT after 12 weeks was numerically reduced at both solifenacin doses, only the 5 mg dose was significant vs placebo; however, BWT measurement variability was high within the dose groups. Measurement variability may be due to differences in bladder filling between visits, differences in afferent signalling to the bladder affecting BWT, variable image quality, BWT measurement difficulties in a completely empty bladder, the use of still ultrasound images for evaluation from what is usually a dynamic investigation, or insufficient standardisation of ultrasound methods. Exploratory analysis (ANCOVA) based on the measurements from the local readers estimated a difference of 0.01 mm in change from baseline for pooled solifenacin versus placebo (95%CI −0.13–0.15 mm). Use of still versus dynamic ultrasound images therefore contributed to the variability, but a separate analysis of the local reader data also showed no statistically significant change in BWT with solifenacin 5 or 10 mg compared to placebo. The lack of dose effect may be related to the fact that solifenacin 5 mg was the most appropriate dosage for the severity of symptoms reported by the majority of patients in the study, with symptoms not being severe enough to warrant an increase to solifenacin 10 mg.

Post hoc analysis in subgroups defined by baseline BWT showed numerically greater reductions in BWT in each treatment arm when only patients with a baseline BWT >5 mm were included; further analysis suggested that regression to the mean due to random variation, a source of bias for the real size of the treatment effect, may explain these results. Results for the >5 mm group are consistent with those from a similar study with tolterodine, where a significant BWT reduction was observed after 12 weeks versus placebo in patients with baseline BWT of >5 mm;[14] however, no patients with BWT ≤5 mm were included in this study for comparison. Recent retrospective evaluation of BWT in men with LUTS included baseline BWT above and below 5 mm,[22] and found BWT reductions from 6.8 to 4.6 mm in a patient subgroup treated with alfuzosin for 12 weeks. It remains unclear whether this result reflects a true effect of treatment on BWT in men, since only patients with baseline BWT >5 mm were treated with alfuzosin and included in this analysis, based on the pretreatment baseline BWT value of 6.8 mm.
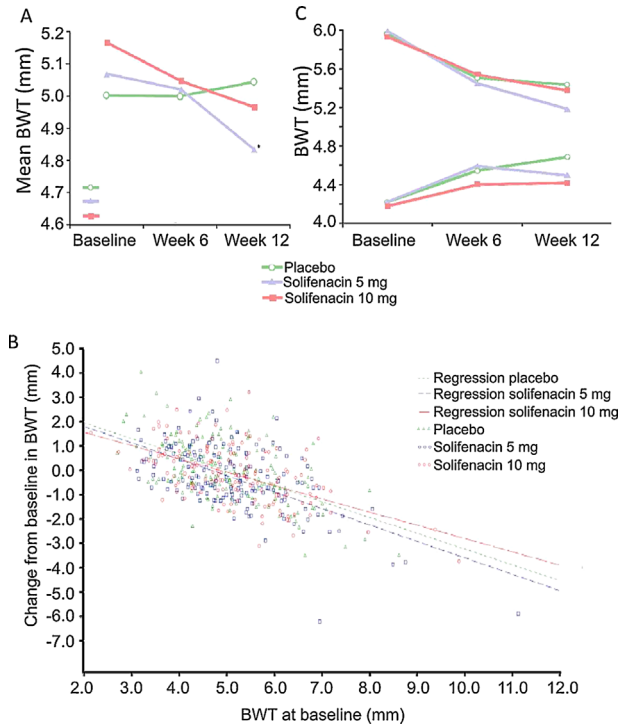
Figure 3. (A) Change in mean BWT (mm) by visit (FAS-BWT), (B) Scatter plot of BWT change from baseline to week 12 (LOCF) versus baseline BWT (mm), with linear regression lines estimated within each treatment arm) (C) Summary of mean change from baseline stratified by baseline category (≤5 mm, >5 mm) by visit (FAS-BWT). **A*** $P < 0.05$ versus placebo. SD values ranged from 1.1 to 1.3 mm. *P*-values indicate results of treatment comparisons based on an ANCOVA model. **B.** Overall, 29–34% of the variability in change from baseline within a treatment arm is explained by the size of the baseline value (Rs = 0.288–0.340). BWT, bladder wall thickness; LOCF, last observation carried forward. **C.** Comparison of change from baseline with solifenacin 5 mg and 10 mg versus placebo subgroups defined by baseline category was not significant (Wilcoxon rank-sum test, $P > 0.05$). SD at Week 12 LOCF ranged from 0.91 to 1.15 mm for absolute values and from 0.92 to 1.43 for change from baseline.

The SHRINK study showed that, although solifenacin significantly improved micturition diary variables and patient-reported outcomes versus placebo, there were no correlations between changes in efficacy variables and BWT. Associations between BWT were observed between some patient-associated factors, e.g. age, weight, parity and perception of disease severity; however, it remains unclear whether these are unique to women with OAB and DO or relate to all women.

While these findings confirm that solifenacin treatment is efficacious in the reduction of OAB symptoms, they cast doubt on a relationship between OAB/DO and BWT measurements. Furthermore, the observed combination of a confirmed urodynamic diagnosis of DO together with a baseline BWT measurement <5 mm does not support the suggested 5 mm cut-off for a diagnosis of DO.

CONCLUSIONS

No clear effect of solifenacin on BWT as measured by TVUS was observed. The substantial variation in BWT in this patient population and the absence of a statistically significant correlation between BWT and symptom severity suggests that BWT is unlikely to be a reliable indicator of DO or response

to solifenacin treatment. Therefore, these results do not support the routine clinical assessment of BWT with TVUS for the diagnosis of DO or the assessment of treatment responses in patients with OAB.

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