Original Article: Clinical Investigation

Efficacy and safety of the noradrenaline reuptake inhibitor, TAS-303, in women with stress urinary incontinence: Results of a double-blind, randomized, placebo-controlled, early phase II trial

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Abbreviations & Acronyms
ADR = adverse drug reaction
AE = adverse event
ALT = alanine aminotransferase
CI = confidence interval
ICIQ-SF = International Consultation on Incontinence Questionnaire – Short Form
IEF = incontinence episode frequency
IQR = interquartile range
MUI = mixed urinary incontinence
o.d. = once daily
PGI-I = Patient Global Impression – Improvement
PPS = per-protocol set
R = randomization
SD = standard deviation
SUI = stress urinary incontinence
UUI = urgency urinary incontinence

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Objective: To carry out an exploratory assessment of the efficacy and safety of TAS-303, a noradrenaline reuptake inhibitor, in women with stress urinary incontinence.

Methods: In a double-blind, placebo-controlled, early phase II study, women with stress urinary incontinence and stress urinary incontinence-predominant mixed urinary incontinence were randomized to a placebo or TAS-303 (3 or 6 mg) once daily for 8 weeks. The main efficacy end-points were mean percentage change in incontinence episode frequency per 24 h from baseline to week 8 (the primary end-point) and week 4.

Results: At week 8, the mean percentage change in incontinence episode frequency per 24 h was −34.73% in the TAS-303 3 mg group, −35.41% in the TAS-303 6 mg group and −28.07% in the placebo group (differences *vs* placebo, not significant). In patients with stress urinary incontinence, or incontinence episode frequency less than two episodes per 24 h at baseline, TAS-303 significantly reduced incontinence episode frequency versus placebo after 4 weeks; some secondary end-points also showed a tendency to improve in the same subgroups. No serious adverse events (e.g. central nervous system or cardiovascular effects) were observed; TAS-303 was well tolerated and had a favorable safety profile.

Conclusion: These findings suggest that TAS-303 is effective for improving stress urinary incontinence symptoms in some subgroups of patients with stress urinary incontinence. Therefore, further research is warranted.

Key words: phase II clinical trial, serotonin and noradrenaline reuptake inhibitors, stress urinary incontinence, women's health.

Introduction

Urinary incontinence is a common, but distressing, condition that becomes more prevalent with increasing age.[1] There are different subtypes of urinary incontinence defined by the symptom pattern and trigger.[2,3] One of the most common forms is SUI,[4] characterized by involuntary leakage of urine during exercise/exertion, or during coughing or sneezing.[2,3] Another common subtype is UUI, in which feelings of urgency are associated with involuntary urine loss.[2] Patients with symptoms of both UUI and SUI are described as having MUI.[2,3] SUI is more common in women than men, affecting 12.6% of Japanese women aged ≥40 years versus just 3.0% of Japanese men in this age group.[5] SUI has a negative impact on quality of life.[6]

In Japan, the only drug approved for the treatment of SUI is clenbuterol, a β_2-agonist. However, adverse effects, such as finger tremor and tachycardia, have been reported,[7] and caution is required when prescribing clenbuterol in patients with hypertension or heart disease.[8] The serotonin noradrenaline reuptake inhibitor, duloxetine, has been extensively studied in SUI.[9] Duloxetine is approved for use in Europe for SUI, but has not been approved for this indication in the USA or Japan, where regulatory agencies have decided that the risks of treatment outweigh its benefits.[10] These risks include a high incidence of nausea leading to discontinuation,[9] and a small increased risk of suicidality and violence.[10,11]

TAS-303 is a noradrenaline reuptake inhibitor that is in development for the treatment of SUI. It has been shown to increase basal urethral pressure and leak point pressure in animal models.[12] The aim of the present study was to carry out an exploratory investigation into the efficacy and safety of two oral doses of TAS-303 (3 or 6 mg) over a period of 8 weeks of treatment in women with SUI.

Methods

The present randomized, double-blind, placebo-controlled, early phase II study was undertaken at 31 centers in Japan between 17 October 2016 and 25 April 2018.

The study was carried out according to the ethical principles of the Declaration of Helsinki, the Pharmaceuticals and Medical Devices Act, and the "Ministerial Ordinance on Good Clinical Practice". The protocol was approved by the institutional review board at each study site, and all patients provided written informed consent before the initiation of any study procedures. The study was registered at ClinicalTrials. gov (registration number: NCT02906683).

Study design

The present study had three periods: (i) a single-blind observation period, during which eligible patients received placebo once daily; (ii) an 8-week active treatment period; and (iii) a post-treatment observation period (Fig. 1). After completion of the observation period, eligible patients were randomized 1:1:1 to receive double-blind treatment with TAS-303 3 mg, 6 mg or matching placebo tablets once daily for 8 weeks. Randomization was undertaken using an interactive web response system and stratified by mean IEF <2 or ≥2 per 24 h at baseline (visit 2) and type of urinary incontinence (SUI or MUI). A follow-up visit was scheduled for 2–4 weeks after treatment completion (i.e. at week 10–12 of the trial).

Study assessments

Patients were asked to visit at weeks 4 and 8 after the start of the double-blind treatment period for physical assessment and laboratory tests (urine and blood), and to complete the PGI-I and ICIQ-SF self-assessment questionnaires. The 1-h pad test was undertaken at enrollment in the observation period, and after 8 weeks of double-blind treatment. Patients were asked to record IEF in a bladder diary throughout the observation and treatment periods; data from these diaries were reviewed at each assessment. AEs and ADRs were assessed throughout the study.

Eligibility criteria

Female outpatients aged 20–80 years were eligible for inclusion if they had experienced symptoms of SUI for ≥12 weeks before enrollment, were capable of keeping an accurate bladder diary without assistance, and met specific incontinence criteria during the observation period. Patients who met these criteria entered the observation period for 3 weeks and completed a bladder diary for 7 days. Key exclusion criteria were having more prominent UUI than SUI symptoms. A list of other exclusion criteria is shown in Table S1.

End-points

The primary end-point was the mean percentage change in IEF per 24 h from baseline to week 8, and this parameter at week 4 was a secondary end-point. Other secondary end-points were the percentage of patients with an incontinence amount of ≤2.0 g in the 1-h pad test at week 8, with an improvement in PGI-I (i.e. patients selecting "very much better," "much better" or "a little better"), and change from baseline in ICIQ-SF total score, week 4 and week 8. Safety was assessed as the number and severity of AEs and ADRs.

Statistical analysis

Based on the duloxetine clinical trial in Asian women with SUI,[13] we assumed that TAS-303 would reduce the mean
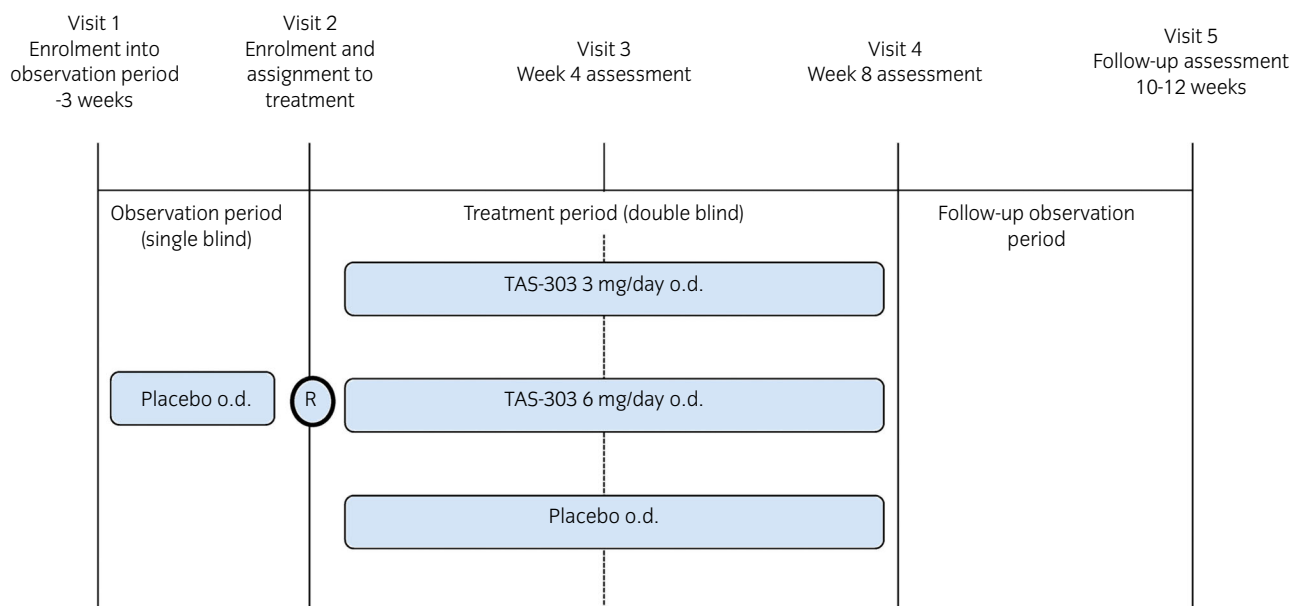

Fig. 1 Study design.

IEF by 20% compared with the placebo, with a SD of 35%. We calculated that a sample size of 250 patients would have 90% power to detect a difference between TAS-303 and the placebo at a two-sided significance level of 0.05, and each test of 2.5% by Bonferroni's method, assuming a 5% dropout rate.

Efficacy analyses were undertaken on the PPS without protocol violations. Safety analyses were carried out on the all-treated population of patients who received study medication during the treatment period.

The primary analysis compared the mean percentage change in IEF per 24 h from baseline in each TAS-303 group versus placebo in the PPS, using a two-sided *t*-test and a 5% significance level. The significance level for each comparison was adjusted for multiplicity using Hochberg's method. The proportion of patients and 95% CIs were calculated for specified changes in incontinence parameters. The percentage of patients with an improvement of PGI-I at enrollment, weeks 4 and 8 in the TAS-303 groups were compared with the placebo using Fisher's exact test; changes from baseline in the ICIQ-SF total score were compared using Student's *t*-test. The primary and secondary end-points were also assessed in groups based on allocation adjustment factors (type of urinary incontinence [SUI or MUI] and mean IEF [<2 or ≥2 per 24 h]). A post-hoc analysis assessed the pooled data from diaries completed during the baseline phase (visits 1 and 2) and both treatment phases (visits 3 and 4), and in subgroups of patients with SUI aged <60 or ≥60 years.[14] All statistical analyses were carried out using SAS statistical software (version 9.4; SAS Institute, Cary, NC, USA).

Results

Overall, informed consent was obtained from 386 patients, 337 entered the first observation period, and 256 were randomized (Fig. 2). The PPS included 245 patients who were aged 33–79 years (mean 56.3 years, SD 12.2 years). Baseline demographics of patients in the PPS are shown in Table 1.

The overall medication compliance rate in the PPS was 99.1% in the observation period and 98.2% in the treatment period.

Primary end-point

In the PPS, the mean percentage change from baseline in IEF per 24 h at week 8 of treatment was not significantly different between either of the TAS-303 groups and the placebo group (Table 2; Fig. 3a).
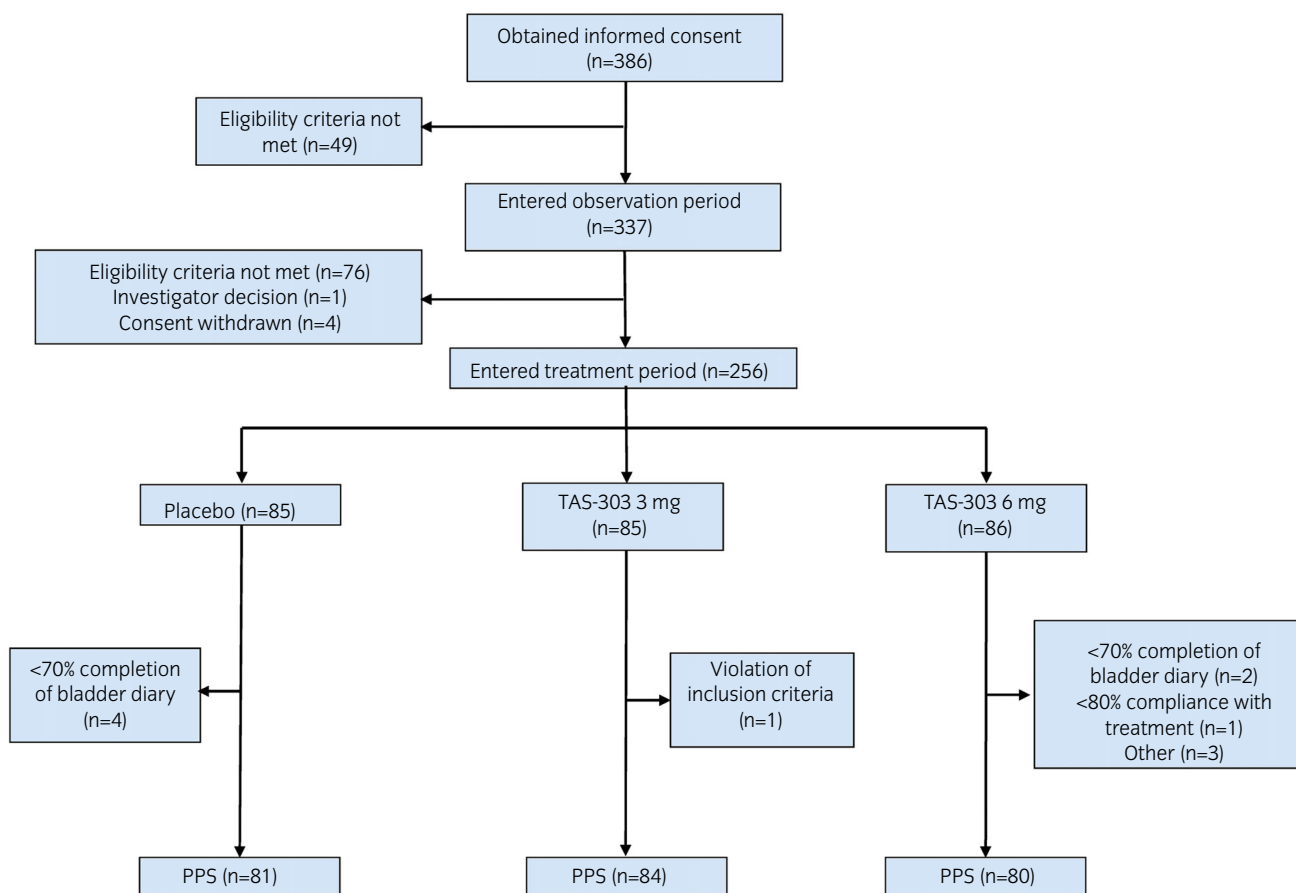

Fig. 2 Patient disposition.

Table 1 Baseline demographic and clinical characteristics

	Placebo (n = 81)	TAS-303 3 mg (n = 84)	TAS-303 6 mg (n = 80)
Mean age, years (SD)	55.9 (11.3)	57.0 (11.8)	56.0 (13.4)
Mean body mass index, kg/m² (SD)	24.6 (3.7)	24.6 (3.7)	24.3 (3.9)
Type of urinary incontinence, n (%)			
SUI	61 (75.3)	63 (75.0)	61 (76.3)
MUI	20 (24.7)	21 (25.0)	19 (23.8)
Prior surgery for pelvic organ prolapse, n (%)	5 (6.2)	10 (11.9)	5 (6.3)
Mean IEF <2 per 24 h, n (%)	41 (50.6)	39 (46.4)	40 (50.0)
Mean IEF ≥2 per 24 h, n (%)	40 (49.4)	45 (53.6)	40 (50.0)
Mean IEF per 24 h (SD)	2.6 (1.7)	2.9 (2.3)	2.5 (1.5)
Mean 1-h pad test weight, g (SD)	37.9 (60.5)	33.9 (71.0)	29.1 (48.3)

Analyses based on the PPS.

Secondary end-points

In the subgroup of patients with SUI (SUI subgroup), the mean percentage change in IEF per 24 h from baseline to week 4 was significantly greater with TAS-303 3 mg and 6 mg than with the placebo ($P < 0.05$; Table 3; Fig. 3b). Furthermore, in the subgroup of patients with baseline IEF <2 per 24 h (IEF <2 subgroup), there was a significantly greater reduction with TAS-303 3 mg (-23.93%; $P < 0.05$) and 6 mg (-31.36%; $P < 0.001$) than the placebo (1.24%) at week 4 (Fig. 4). However, in the subgroups of patients with MUI (MUI subgroup) or with baseline IEF ≥2 per 24 h (IEF ≥2 subgroup), or at week 8 in any of the subgroups, there were no significant differences between either of the TAS-303 groups and the placebo (Figs 3b,c and 4). The pooled diary analysis showed a significant difference between the placebo and both TAS-303 groups for change from baseline in IEF per 24 h in the SUI group (Table 3), but there was no difference between the placebo and TAS-303 groups in the pooled diary analysis of the PPS (Table 2).

No significant differences in the percentage change in IEF between TAS-303 and the placebo were seen in patients aged <60 years or ≥60 years, except in the subgroup of patients aged ≥60 years with SUI who, at 8 weeks, had a significantly greater decrease in IEF with either dose of TAS-303 than with the placebo (Fig. S1).

There was a trend toward a higher percentage of patients with a 1-h pad test result of ≤2.0 g at week 8 in the group receiving TAS-303 6 mg and 3 mg compared with the placebo in the PPS or any of the subgroups; however, there was no significant difference in the PPS population or any of the other subgroups (Table 4).

In the IEF <2 subgroup, significantly more patients in the TAS-303 6 mg group reported improvement on the PGI-I at week 4 compared with the placebo group ($P = 0.009$;

Table 2 IEF per 24 h

	Placebo	TAS-303 3 mg	TAS-303 6 mg
Baseline	n = 81	n = 84	n = 80
Mean (SD)	2.6 (1.7)	2.9 (2.3)	2.5 (1.5)
Median (IQR)	1.9 (1.4, 3.3)	2.1 (1.3, 3.5)	1.9 (1.4, 3.3)
Week 4	n = 81	n = 83	n = 79
Mean (SD)	2.2 (1.7)	2.3 (2.2)	2.0 (1.5)
Median (IQR)	1.7 (1.0, 2.4)	1.4 (0.9, 3.0)	1.4 (0.9, 3.0)
Mean percentage change in IEF per 24 h from baseline (SD)	−11.7 (45.4)	−23.1 (37.3)	−23.9 (33.8)
Median percentage change in IEF per 24 h from baseline (IQR)	−14.1 (−45.2, 14.3)	−22.2 (−52.9, 0.0)	−28.6 (−50.0, −5.0)
Difference vs placebo for mean percentage change in IEF per 24 h from baseline (95% CI)		−11.3 (−24.1, 1.5)	−12.1 (−24.7, 0.4)
P-value†		0.082	0.057
Week 8	n = 81	n = 84	n = 80
Mean (SD)	1.9 (1.9)	2.0 (2.3)	1.7 (1.7)
Median (IQR)	1.1 (0.7, 2.3)	1.1 (0.7, 2.4)	1.1 (0.6, 2.3)
Mean percentage change in IEF per 24 h from baseline (SD)	−28.1 (47.3)	−34.7 (39.9)	−35.4 (39.0)
Median percentage change in IEF per 24 h from baseline (IQR)	−32.3 (−66.7, 7.1)	−42.9 (−64.3, −14.2)	−36.2 (−69.0, −11.6)
Difference vs placebo for mean percentage change in IEF per 24 h from baseline (95% CI)		−6.7 (−20.1, 6.7)	−7.3 (−20.9, 6.2)
P-value†		0.329	0.285
Pooled diary analysis‡	n = 81	n = 84	n = 80
Mean (SD)	2.0 (1.7)	2.2 (2.2)	1.9 (1.5)
Median (IQR)	1.4 (0.9, 2.5)	1.3 (0.8, 2.5)	1.3 (0.8, 2.8)
Mean percentage change in IEF per 24 h from baseline (SD)	−19.9 (43.0)	−28.7 (35.2)	−29.8 (29.7)
Median percentage change in IEF per 24 h from baseline (IQR)	−21.1 (−58.3, 5.3)	−28.6 (−54.8, −13.8)	−27.7 (−53.7, −8.71)
Difference vs placebo for mean percentage change in IEF per 24 h from baseline (95% CI)		−8.8 (−20.9, 3.2)	−9.9 (−21.4, 1.6)
P-value†		0.15	0.09

Analyses based on the PPS. †P-value versus placebo of mean percentage change in IEF per 24 h from baseline (Student's t-test). ‡Analysis of percentage change in IEF was carried out using the baseline diaries and the pooled data of two treatment-phase diaries (weeks 4 and 8).
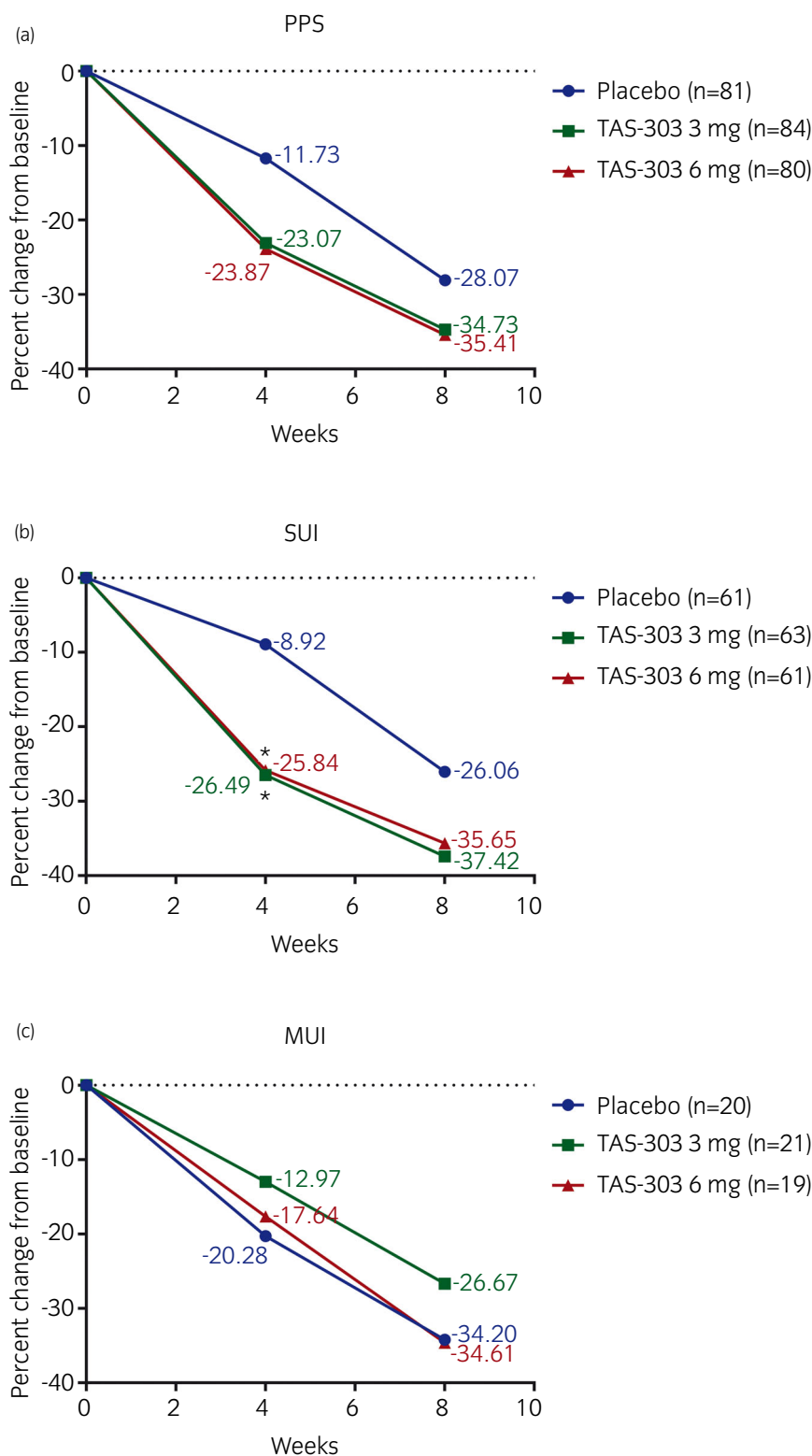
(a)

PPS

(b)

SUI

(c)

MUI

Fig. 3 Percentage change from baseline in mean IEF in the (a) PPS, (b) SUI subgroup and (c) MUI subgroup. *$P < 0.05$ versus placebo.

Table 4). At week 8, slightly more patients in the TAS-303 groups than the placebo groups showed an improvement in PGI-I in the PPS and most of the subgroups, but the differences were not statistically significant for TAS-303 versus placebo.

Regarding ICIQ-SF total scores, the mean changes from baseline at weeks 4 and 8 showed a tendency for changes to be larger in the TAS-303 groups versus the placebo group, but differences were generally not statistically significant (Table S2).

Safety

The percentage of patients with any AE was similar in the three groups, and nasopharyngitis was the most common AE in all

Table 3 IEF per 24 h in patients with SUI

	Placebo	TAS-303 3 mg	TAS-303 6 mg
Baseline	*n* = 61	*n* = 63	*n* = 61
Mean (SD)	2.6 (1.7)	2.7 (2.4)	2.5 (1.5)
Median (IQR)	1.9 (1.4, 3.3)	2.0 (1.1, 3.4)	2.0 (1.3, 3.4)
Week 4	*n* = 61	*n* = 62	*n* = 60
Mean (SD)	2.3 (1.9)	2.0 (1.9)	1.9 (1.5)
Median (IQR)	1.7 (1.0, 2.9)	1.4 (0.9, 2.1)	1.4 (0.7, 3.0)
Mean percentage change of IEF per 24 h from baseline (SD)	−8.9 (46.3)	−26.5 (34.8)	−25.8 (33.5)
Median percentage change of IEF per 24 h from baseline (IQR)	−13.3 (−41.7, 14.3)	−22.2 (−55.6, −8.0)	−30.9 (−50.0, −5.3)
Difference *vs* placebo for mean percentage change in IEF per 24 h from baseline (95% CI)		−17.6 (−32.2, −3.0)	−16.9 (−31.5, −2.3)
P-value†		0.019	0.023
Week 8	*n* = 61	*n* = 63	*n* = 61
Mean (SD)	2.0 (2.0)	1.8 (2.1)	1.8 (1.8)
Median (IQR)	1.1 (0.7, 2.3)	1.1 (0.7, 2.3)	1.1 (0.6, 2.4)
Mean percentage change of IEF per 24 h from baseline (SD)	−26.1 (47.8)	−37.4 (33.1)	−35.7 (37.8)
Median percentage change of IEF per 24 h from baseline (IQR)	−30.0 (−63.9, 7.1)	−42.9 (−64.3, −18.2)	−35.71 (−65.0, −12.0)
Difference *vs* placebo for mean percentage change in IEF per 24 h from baseline (95% CI)		−11.4 (−25.9, 3.2)	−9.6 (−25.1, 5.9)
P-value†		0.125	0.221
Pooled diary analysis‡	*n* = 61	*n* = 63	*n* = 61
Mean (SD)	2.1 (1.9)	1.9 (2.0)	1.9 (1.6)
Median (IQR)	1.4 (0.9, 2.9)	1.3 (0.7, 2.1)	1.1 (0.8, 3.0)
Mean percentage change of IEF per 24 h from baseline (SD)	−17.5 (43.1)	−31.7 (30.6)	−31.0 (30.1)
Median percentage change of IEF per 24 h from baseline (IQR)	−14.7 (−57.1, 5.3)	−28.6 (−55.2, −15.5)	−29.2 (−56.3, −9.1)
Difference *vs* placebo for mean percentage change in IEF per 24 h from baseline (95% CI)		−14.2 (−27.5, −0.9)	−13.5 (−26.8, −0.1)
P-value†		0.036	0.048

†*P*-value versus placebo of mean percentage change in IEF per 24 h from baseline (Student's *t*-test). ‡Analysis of percentage change in IEF was carried out using the last-visit diary entry from the baseline diary, and for pooled diary data from weeks 4 and 8 in the treatment phase.

groups (Table 5). No patient in any group had a serious AE. One patient discontinued TAS-303 6 mg because of fractures in her radius and lumbar spine as a result of a fall, which was assessed as having no causal relationship with TAS-303 by the investigator.

Six patients (7.1%) in the TAS-303 3 mg group had a total of seven ADRs (Table 6). These ADRs were mainly changes in laboratory parameters, constipation and rash. All but one were mild in severity, and all resolved without treatment. No ADRs occurred in the TAS-303 6 mg or placebo groups; no clinically relevant changes in electrocardiogram parameters or vital signs, nor any nervous system ADRs, were recorded during the study.

Discussion

In the present study, the mean percentage decrease in IEF per 24 h from baseline to week 8 was approximately 7% greater with TAS-303 3 mg and 6 mg compared with the placebo, but the differences were not statistically significant. However, in the SUI subgroup and IEF <2 subgroup, there was a greater reduction in IEF in both TAS-303 dose groups compared with the placebo at week 4, and in the pooled diary analysis.

In the present study, the effect of TAS-303 was less marked in patients with MUI. This is likely to be because MUI includes components of UUI.[2,3] In SUI, urethral resistance and urethral pressure are low, so that a small increase in intravesical pressure overrides urethral resistance, leading to urine leakage.[15] Whereas SUI is principally a disorder of the urethra, UUI is a disorder of the detrusor in which involuntary contractions occur during bladder filling, leading to urgency and leakage/incontinence.[16] These involuntary contractions arise from disturbances in smooth muscle and urothelium, or central nervous system dysfunction associated with urgency, in which the normal limbic mechanism for maintaining continence becomes less effective at suppressing micturition, and the parasympathetic voiding reflex is easily activated.[17] Therefore, patients with UUI might not be appropriate to properly assess the efficacy of a noradrenaline reuptake inhibitor.

Similarly, the difference between TAS-303 and the placebo regarding change in ICIQ-SF score was not significant, probably because the ICIQ-SF questionnaire also includes UUI symptoms.

A marked response to TAS-303 was observed in the IEF <2 subgroup, excluding patients with severe SUI (arbitrarily defined as IEF ≥2 per 24 h at baseline[14]). In this subgroup, some secondary end-points, such as the percentage of patients with the improvement rate of PGI-I, suggested a statistically significant improvement compared with the placebo. These results imply that the appropriate target population for TAS-303 is patients with mild or moderate incontinence.
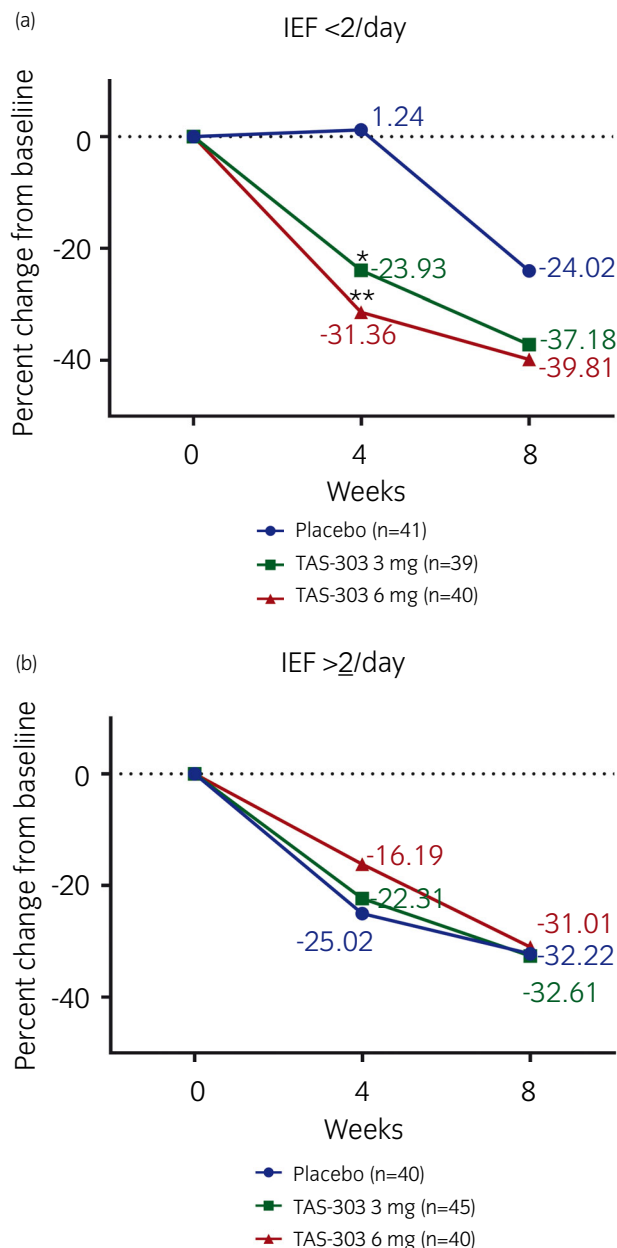
(a)

(b)

Fig. 4 Percentage change from baseline in mean IEF in patients with (a) IEF <2 per 24 h at baseline and (b) IEF ≥2 per day at baseline. *P < 0.05 versus placebo; **P < 0.001 versus placebo.

Table 4 Effect of TAS-303 on incontinence volume and patient assessment of improvement at weeks 4 and 8

	Placebo	TAS-303 3 mg	TAS-303 6 mg
PPS population	n = 81	n = 84	n = 80
Incontinence volume ≤2.0 g in 1-h pad test at week 8, n (%)	13 (16.0)	25 (29.8)	27 (33.8)
PGI-I improvement,† n (%)			
Baseline	26 (32.1)	28 (33.3)	29 (36.3)
Week 4	44 (54.3)	49 (58.3)	58 (72.5)*
Week 8	53 (65.4)	61 (72.6)	55 (68.8)
SUI group	n = 61	n = 63	n = 61
Incontinence volume ≤2.0 g in 1-h pad test at week 8, n (%)	10 (16.4)	18 (28.6)	17 (27.9)
PGI-I improvement,† n (%)			
Baseline	19 (31.1)	18 (28.6)	21 (34.4)
Week 4	33 (54.1)	35 (55.6)	44 (72.1)
Week 8	39 (63.9)	43 (68.3)	41 (67.2)
MUI group	n = 20	n = 21	n = 19
Incontinence volume ≤2.0 g in 1-h pad test at week 8, n (%)	3 (15.0)	7 (33.3)	10 (52.6)
PGI-I improvement,† n (%)			
Baseline	7 (35.0)	10 (47.6)	8 (42.1)
Week 4	11 (55.0)	14 (66.7)	14 (73.7)
Week 8	14 (70.0)	18 (85.7)	14 (73.7)
IEF <2 per 24 h‡	n = 41	n = 39	n = 40
Incontinence volume ≤2.0 g in 1-h pad test at week 8, n (%)	6 (14.6)	12 (30.8)	19 (47.5)
PGI-I improvement,† n (%)			
Baseline	15 (36.6)	11 (28.2)	17 (42.5)
Week 4	17 (41.5)	24 (61.5)	30 (75.0)**
Week 8	23 (56.1)	27 (69.2)	28 (70.0)
IEF ≥2 per 24 h§	n = 40	n = 45	n = 40
Incontinence volume ≤2.0 g in 1-h pad test at week 8, n (%)	7 (17.5)	13 (28.9)	8 (20.0)
PGI-I improvement,† n (%)			
Baseline	11 (27.5)	17 (37.8)	12 (30.0)
Week 4	27 (67.5)	25 (55.6)	28 (70.0)
Week 8	30 (75.0)	34 (75.6)	27 (67.5)

Results are shown for the PPS and for subgroups of patients defined by diagnosis (SUI vs MUI) and baseline IEF (<2 vs ≥2 per 24 h). †Defined as answering "very much better," "much better" or "a little better" on the PGI-I questionnaire. ‡Defined as patients with mean IEF less than twice per 24 h at baseline. §Defined as patients with mean incontinence episodes frequency twice or more per 24 h at baseline. *P < 0.05 versus placebo. **P = 0.009 versus placebo.

Whereas, in the SUI or IEF <2 subgroup, the mean percentage change in IEF was a low placebo effect at week 4, thus the difference between the placebo and the TAS-303 groups was large and there was a significant difference. In contrast, there was a marked placebo effect at week 8, reducing the difference between the TAS-303 groups and the placebo (Figs 3b,4a). Therefore, in evaluating the percentage change in IEF, it is necessary to plan a study design that suppresses the placebo effect.

In patients aged ≥60 years with SUI, the mean percentage change in IEF was significantly greater with both doses of TAS-303 than with the placebo. Thus, the effect of TAS-303 treatment might be more evident in older patients with SUI; this could be because maximum urethral closure pressure decreases with age.[18]

In addition to the target population discussed above, other factors might have contributed to the lack of a significant difference in the primary end-point. First, there was considerable variability in the mean percentage change in IEF from baseline at week 8. At the planning, we assumed a SD of 35% based on the previous duloxetine study;[13] in this study, it

Table 5 AEs occurring in ≥2% of patients during the treatment period

Events, n (%)	Placebo (n = 85)	TAS-303 3 mg (n = 85)	TAS-303 6 mg (n = 86)
Any adverse event	26 (30.6)	31 (36.5)	20 (23.3)
Nasopharyngitis	8 (9.4)	9 (10.6)	4 (4.7)
Cystitis	1 (1.2)	2 (2.4)	0
Constipation	0	2 (2.4)	1 (1.2)
Diarrhea	0	0	2 (2.3)
Decreased appetite	0	0	2 (2.3)
Headache	0	0	2 (2.3)
Cough	0	0	2 (2.3)
ALT increased	0	2 (2.4)	0
Eczema	2 (2.4)	0	0

was 39.0–47.3%, with the placebo group being especially high. The assessment of urinary incontinence is influenced by inherent variability of IEF, as measured by a bladder diary,[19] and the effect of self-monitoring on bladder habits.[20] Pooling bladder diaries reduced the intra-subject variability in IEF by approximately 50%.[14] Similarly, in the present study, the pooled diary analysis, which combined the data at weeks 4 and 8, showed a decrease in the SD of the mean percentage change in IEF.

Second, the dose of TAS-303 used in the current study might have been suboptimal. The 3-mg dose used in the present study was extrapolated from the dose identified as effective in animal studies, but we also included a 6-mg dose to examine the dose–response of TAS-303 in an exploratory manner; a 6-mg dose was confirmed to be safe for multiple-dose administration at the planning. However, preclinical data suggest that a TAS-303 dose of 18 mg is required to produce noradrenaline reuptake inhibition equivalent to that achieved with the recommended dose of duloxetine.[12] Such a dose has been clinically investigated, and no additional safety concerns were identified;[21,22] therefore, an exploratory study using a higher dose might need to be considered.

TAS-303 does not inhibit serotonin reuptake, and serotonergic adverse effects are therefore unlikely. Furthermore, a

pharmacokinetic study using radiolabeled TAS-303 confirmed that it does not enter the brain, and is therefore unlikely to cause central AEs.[12] In this study, ADRs occurred only in patients receiving TAS-303 3 mg, and were mostly mild elevations in laboratory tests. The only symptomatic ADRs were rash and constipation; the latter was of moderate severity, but all other ADRs were mild. These data suggest that TAS-303 is well tolerated and has a favorable safety profile.

In conclusion, TAS-303 3 mg and 6 mg had a favorable safety profile in the present study, and there was a trend toward improvement of SUI with TAS-303 relative to the placebo for some subgroups. These results suggest that TAS-303 might provide an effective and well tolerated treatment option for SUI, especially in patients with mild or moderate disease. TAS-303 is worthy of additional research in SUI, and the findings of this early phase II study will improve the design of future studies.

Acknowledgments

Conflict of interest

ST, MT, OY and MG report grants and consultancy fees from Taiho. KK reports consultancy fees from Taiho relating to this study. ST reports grants and personal fees from Astellas, Pfizer, Kissei, Kyorin and Nippon-shinyaku. KK reports personal fees from Unicharm, Pfizer, Astellas and Kissei. MT reports personal fees from Astellas, Pfizer, Kyorin, Ono, Hisamitsu, Nippon-shinyaku, Takeda, Ferring and Kissei. OY reports financial interests and/or other relationships with Kissei, Pfizer, Astellas, GlaxoSmithKline and Nippon-shinyaku. MG reports grants and personal fees from Astellas, Ono, Kissei, Kyorin, Sanofi, Daiichi-Sankyo, Takeda and Chugai.

Table 6 Adverse drug reactions

MedDRA version 21.0 System organ class Preferred term	Placebo (n = 85) Any severity	TAS-303 3 mg (n = 85)			TAS-303 6 mg (n = 86) Any severity
		Mild	Moderate	Severe	
Any events	0	5 (5.9)	1 (1.2)	0	0
Gastrointestinal disorders	0	0	1 (1.2)	0	0
Constipation	0	0	1 (1.2)	0	0
Investigations	0	4 (4.7)	0	0	0
ALT increased	0	1 (1.2)	0	0	0
Aspartate aminotransferase increased	0	1 (1.2)	0	0	0
Blood creatinine phosphokinase increased	0	1 (1.2)	0	0	0
White blood cell count increased	0	1 (1.2)	0	0	0
Liver function test increased	0	1 (1.2)	0	0	0
Skin and subcutaneous tissue disorders	0	1 (1.2)	0	0	0
Rash	0	1 (1.2)	0	0	0

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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. Percentage change from baseline in mean IEF in patients. (a) Aged <60 years; (b) aged ≥60 years; (c) with SUI aged <60 years; and (d) with SUI aged ≥60 years. *$P < 0.05$ versus placebo.

Table S1. Exclusion criteria.

Table S2. ICIQ-SF total scores and changes from baseline at weeks 4 and 8, both in the PPS and for subgroups defined by type and severity of incontinence.