

# Results of a randomized, double-blind, active-controlled clinical trial with propiverine extended release 30 mg in patients with overactive bladder

Jing Leng<sup>\*</sup>, Limin Liao<sup>†</sup>, Ben Wan<sup>‡</sup>, Chuanjun Du<sup>§</sup>, Wei Li<sup>¶</sup>, Keji Xie<sup>\*\*</sup>, Zhoujun Shen<sup>††</sup>, Zhuoqun Xu<sup>‡‡</sup>, Shiliang Wu<sup>§§</sup>, Zujun Fang<sup>¶¶</sup>, Lulin Ma<sup>\*\*\*</sup>, Shaomei Han<sup>†††</sup>, Cornelia Feustel<sup>‡‡‡</sup>, Yong Yang<sup>§§§</sup> and Helmut Madersbacher<sup>¶¶¶</sup>

<sup>\*</sup>Renji Hospital Affiliated to Shanghai JiaoTong University School of Medicine, Shanghai, <sup>†</sup>Beijing Boai Hospital, Beijing, <sup>‡</sup>Beijing Hospital of the Ministry of Health, Beijing, <sup>§</sup>Second Affiliated Hospital Zhejiang University College of Medicine, Zhejiang, China, <sup>¶</sup>Second Hospital of Hebei Medical University, Shijiazhuang, China, <sup>\*\*</sup>Guangzhou First Municipal People's Hospital, Guangzhou, China, <sup>††</sup>Ruijin Hospital Affiliated to Shanghai JiaoTong University School of Medicine, Shanghai, <sup>‡‡</sup>Wuxi People's Hospital, Wuxi, China, <sup>§§</sup>Peking University First Hospital, Beijing, <sup>¶¶</sup>Huashan Hospital Affiliated to Fudan University, Shanghai, China, <sup>\*\*\*</sup>Peking University Third Hospital, Beijing, <sup>†††</sup>Basic Medicine Institute of China Academy of Chinese Medical Sciences, Beijing, <sup>‡‡‡</sup>Consultant for APOGEPHA Arzneimittel GmbH, Dresden, Germany, <sup>§§§</sup>Beijing Chaoyang Hospital affiliating Capital University of Medical Sciences, Beijing, China, and <sup>¶¶¶</sup>Medical University Innsbruck, Innsbruck, Austria

The study was registered at clinicaltrials.gov (NCT01512004).

## Objective

To compare the efficacy and safety of the 30 mg extended release (ER) formulation of propiverine hydrochloride with the 4 mg ER formulation of tolterodine tartrate in patients with overactive bladder (OAB) in a non-inferiority trial.

## Patients and Methods

Eligible patients, aged 18–75 years and with symptoms of OAB, were enrolled in this multicentre, randomized, double-blind, parallel-group, active-controlled study. After a 2-week screening period, patients were randomized at a 1:1 ratio to receive either propiverine ER 30 mg or tolterodine ER 4 mg daily during the 8-week treatment period. Efficacy was assessed using a 3-day voiding diary and patient's self-reported assessment of treatment effect. Safety assessment included recording of adverse events, laboratory test results, measurement of post-void residual urine and electrocardiograms.

## Results

A total of 324 patients (244 female and 80 male) were included in the study. Both active treatments improved the variables included in the voiding diary and in the patient's self-reported assessment. **The change from baseline in the number of**

**voidings per 24 h was significantly greater in the propiverine ER 30 mg group compared with the tolterodine ER 4 mg group after 8 weeks of treatment (full analysis set [FAS]  $-4.6 \pm 4.1$  vs  $-3.8 \pm 5.1$ ;  $P = 0.005$ ). Significant improvements were also observed for the change of urgency incontinence episodes after 2 weeks ( $P = 0.026$ ) and 8 weeks ( $P = 0.028$ ) of treatment when comparing propiverine ER 30 mg with tolterodine ER 4 mg. Both treatments were well tolerated, with a similar frequency of adverse drug reactions in both the propiverine ER 30 mg and tolterodine ER 4 mg groups (FAS 40.7 vs 39.5%;  $P = 0.8$ ). More patients treated with tolterodine ER 4 mg discontinued the treatment because of adverse drug reactions compared with propiverine ER 30 mg (7.4 vs 3.1%).**

## Conclusions

Propiverine ER 30 mg was confirmed to be an effective and well-tolerated treatment option for patients with OAB symptoms. This first head-to-head study showed non-inferiority of propiverine ER 30 mg compared with tolterodine ER 4 mg.

## Keywords

overactive bladder, propiverine hydrochloride ER 30 mg, tolterodine ER 4 mg, randomized controlled trial

## Introduction

Even though the diagnostic approach with regard to bladder storage symptoms has improved over the past decades and new treatment options have been developed, overactive

bladder (OAB) is still a disorder that affects the quality of life of millions of people all over the world. Although prevalence rates have been overestimated in the past, current studies suggest a worldwide prevalence rate between 8 and 17% in adults, with incidence increasing with age [1–9]. The

prevalence of OAB in a European population-based study was 3.4% for men and 8.7% for women aged at least 40 years, increasing to 41.9 and 31.3% at the age of 75 years, respectively [10].

Interestingly, the prevalence rates in China seem to be much lower [11,12] because the awareness of LUTS and the potential treatment options in the mainland are not as widespread there. These data are consistent with the estimation obtained by a large-scale epidemiological study from the Chinese Urological Association that assessed OAB symptoms based on the 2002 Standardization Terminology from the International Continence Society [13], and indicated an overall incidence of OAB in the adult population of 6.0% [11]. In contrast, a recently published population-based survey of the prevalence of LUTS in adult Chinese women showed a high prevalence of frequency and urgency of 17.3 and 23.3%, respectively, with a difference between urban and rural women [14]; urban women experienced significantly more frequency and urgency episodes ( $P < 0.001$ ).

These data confirm the necessity to improve the treatment options for LUTS, especially in the elderly population, focusing on treatment adherence and tolerability because concomitant diseases, multiple drug therapies and cognitive function disorders also increase with age.

Treatment adherence and tolerability can be improved with medicinal products that have to be applied only once daily and ensure a more constant drug level. For propiverine, the bioavailability of the extended release (ER) formulation compared with the immediate release (IR) formulation is improved because of a lower rate of biotransformation of the drug substance in more distal segments of the small intestine and more constant absorption rates in the colon [15,16]. Two pharmacokinetic studies with propiverine ER 30 mg were conducted confirming no food effect [17].

Besides lifestyle modification, behavioural therapies and bladder training, antimuscarinic drug therapy is still the main treatment option for OAB. Even though various antimuscarinics are currently available, therapeutic effect and tolerability differs individually in the intended population, not

least because of differences in muscarinic receptor selectivity or in the mode of action. Propiverine differs from other antimuscarinics because of a dual mode of action, with additional effects on calcium homeostasis [18–20].

Effectiveness and tolerability of propiverine in the White and Japanese population has been shown repeatedly [21–27]. In Japan and Korea, a 20 mg IR formulation that is applied once daily served as an active comparator in randomized controlled studies with solifenacin 5 and 10 mg once daily or 0.1 mg imidafenacin twice daily, demonstrating similar efficacy and tolerability [21,27,28].

A multicentre, randomized, double-blind trial compared the IR formulation of propiverine (15 mg coated tablets, twice daily) with tolterodine IR (2 mg tablets, twice daily) in the treatment of OAB, and reported similar improvements in bladder function in terms of cystometric variables, overall quality of life and tolerability [22]. A further placebo- and active-controlled clinical trial in a white population confirmed non-inferiority of propiverine ER to the IR formulation and superiority of both formulations compared with placebo [23].

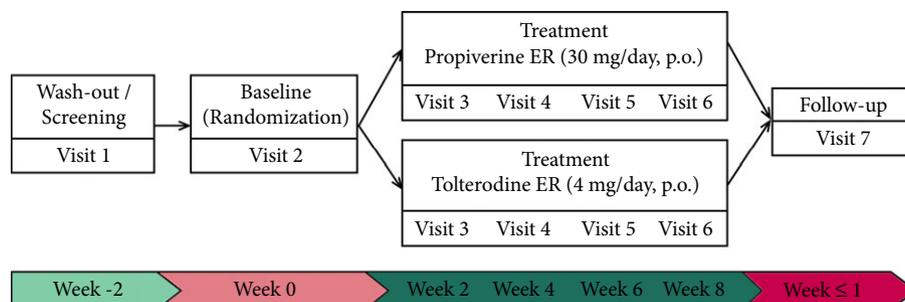
The present non-inferiority trial was designed to compare the efficacy and tolerability of propiverine hydrochloride ER 30 mg (henceforth referred to as propiverine ER) with tolterodine tartrate 4 mg ER (henceforth referred to as tolterodine ER) in patients with OAB.

## Patients and Methods

Male and female patients, aged between 18 and 75 years with OAB symptoms for at least 3 months, were enrolled in the present study. The main inclusion criteria at visit 1 covered urgency episodes with or without urgency incontinence, increased frequency of at least eight voids per 24 h, and a mean voided volume per single micturition of <200 mL within the 3-day voiding diary period before randomization (Fig. 1). The key exclusion criteria included stress urinary incontinence, BOO, acute or recurrent UTIs, idiopathic haematuria and ongoing OAB therapy.

The present randomized multicentre, double-blind, double-dummy, parallel-group and active-controlled clinical trial was

**Fig. 1** Study design. ER, extended release; p.o., orally.



conducted between July 2009 and August 2011 in 11 Chinese hospitals. The study design was approved by the Ethics Committees of the involved hospitals, and was performed in compliance with the ethical principles of the Declaration of Helsinki (2008) and Good Clinical Practice guidelines. Before entering the study, all patients signed informed consent forms.

After a 2-week screening period, eligible patients were randomized at a 1:1 ratio, either to propiverine ER or to tolterodine ER once daily at visit 2. To maintain the blinding, all patients received one capsule (propiverine or matching placebo) and one tablet (tolterodine or matching placebo) daily.

Efficacy was assessed using the completed 3-day voiding diary that was filled in during the last 3 days before baseline (visit 2), at the end of treatment week 2 (visit 3), and after 8 weeks of treatment at visit 6 (Fig. 1).

The primary efficacy endpoint was the change from baseline in the mean number of voidings per 24 h after 8 weeks of treatment. To investigate potential multicentre effects between propiverine ER and tolterodine ER, ANCOVA was performed. Secondary efficacy endpoints included changes from baseline in the mean number of urinary incontinence episodes per 24 h and the mean voided volume per single micturition after 2 and 8 weeks of treatment, the mean number of voidings per 24 h after 2 weeks of treatment, and the time of onset of a therapeutic effect. Additionally, the patient's self-assessment of benefit from treatment was assessed every 2 weeks when the patients visited the study site and received new trial medication (visits 2–5). The ranking level showed three groups: no effect, small effect and large treatment effect, whereas assessment was based on patients' subjective perception.

Tolerability was assessed by recording adverse events (visits 3–7) and vital signs (all visits) (Fig. 1). Additionally, laboratory tests (visits 1, 3 and 6) and 12-lead electrocardiograms (ECGs) were performed, and post-void residual urine was measured via abdominal ultrasonography at screening and end of treatment.

Statistical analyses of efficacy were performed on the full analysis set (FAS) and per-protocol (PP) population. The FAS included all patients who met the inclusion criteria, received at least one dose of the study medication, and whose efficacy was evaluated at least once. The last-observation-carried-forward method was applied for missing values. The PP population comprised all patients who terminated the study according to study protocol. Patients who took at least one dose of the study medication were included in the safety analysis.

To confirm non-inferiority of propiverine ER 30 mg to tolterodine ER 4 mg, the number of required patients was

calculated with 141 per group (282 in total) using previous study results with a non-inferiority margin of 1.0 at a significance level of 0.05 and a power of 80%. The two-sided 95% CI was defined for the changes at 8 weeks from baseline in the mean number of voidings per 24 h. Descriptive analyses of baseline demographic and clinical characteristics were performed. Numerical variables between the groups were compared using *t*-tests and Wilcoxon's test. Changes in categorical variables between the two groups were compared using a chi-squared test and Fisher's exact test. Changes in continuous variables and categorical variables within treatment groups were analysed using paired *t*-tests and Wilcoxon's signed-rank tests. All statistical tests were two-sided, with a significance level of 0.05. SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA) was used for statistical calculations.

## Results

### Subjects

A total of 324 patients (244 women, 80 men, mean age 50 years) with OAB symptoms were enrolled and randomly allocated in 11 study sites. All 324 patients were included in the FAS and safety analysis. The treatment groups did not differ significantly in their demographic or clinical characteristics at baseline (Table 1).

Altogether, 37 patients were excluded from the PP population for the reasons shown in Fig. 2; 16 (4.9%) patients were suspended because of protocol violations and lost to follow-up and one patient withdrew informed consent. Another 17 (5.2%) patients dropped out as a result of adverse events. After 2 weeks of treatment, 158 patients were treated with propiverine ER and 152 patients with tolterodine ER. The PP population after 8 weeks of treatment consisted of 287 patients (148 in the propiverine ER and 139 in the tolterodine ER group). The overall discontinuation rate did not differ significantly between the treatment groups ( $P = 0.12$ ).

### Efficacy

The efficacy results for the FAS (Table 2) showed that for all but one the outcomes did not differ between treatment groups. Furthermore, results were similar for the FAS and PP population. For the patient's self-assessment of treatment effect after 8 weeks, only the FAS population showed a significantly superior benefit from the propiverine treatment compared with the tolterodine treatment ( $P = 0.007$ ); therefore, hereafter, only the FAS results are presented in detail.

The mean number of voidings per 24 h significantly decreased from baseline to the end of treatment in both

**Table 1** Baseline characteristics of patients included in the full analysis set.

Characteristic	Propiverine ER 30 mg (n = 162)	Tolterodine ER 4 mg (n = 162)	P*
Mean (SD) age, years	50.9 (15.9)	49.1 (14.7)	0.3141
Sex			
Male, n (%)	41 (25.3)	39 (24.1)	0.7967
Female, n (%)	121 (74.7)	123 (75.9)	
Physical dimensions, mean (SD)			
Height, cm	162.2 (6.8)	162.2 (7.6)	0.9693
Weight, kg	61.4 (9.9)	60.1 (10.4)	0.2768
BMI, kg/m <sup>2</sup>	23.3 (3.3)	22.8 (3.2)	0.1642
Married			
No, n (%)	20 (12.3)	14 (8.6)	0.2768
Yes, n (%)	142 (87.7)	148 (91.4)	
Past medication			
No, n (%)	145 (89.5)	144 (88.9)	
Yes, n (%)	17 (10.5)	18 (11.1)	
Voiding characteristics			
Urinary frequency, n (%)	162 (100)	162 (100)	–
Urgency, n (%)	155 (95.7)	155 (95.7)	–
Urinary incontinence, n (%)	60 (37.0)	48 (29.6)	0.1573
Urge urinary incontinence	47 (29.0)	41 (25.3)	0.4536
Mixed urinary incontinence	13 (8.0)	7 (4.3)	0.1660
Mean (SD) no. of voidings/24 h	15.2 (5.8)	14.7 (6.0)	0.2132
Mean (SD) no. of urinary incontinence/24 h	1.3 (3.1)	0.6 (1.6)	0.2251
Mean (SD) voided volume, mL	98.9 (43.1)	106.1 (39.6)	0.1216

ER, extended release. \*Categorical data were compared between the two groups using chi-squared test or Fisher's exact test; comparison between groups of quantitative data used t-tests.

treatment groups ( $P < 0.001$ ); however, the decrease in voiding frequency was more pronounced in the propiverine group ( $P = 0.005$ ; Fig. 3). To exclude potential multicentre effects between propiverine ER and tolterodine ER, ANCOVA was performed, resulting in a mean difference for the number of voidings per 24 h of  $-0.55$  (95% CI  $-1.3, 0.2$ ) in favour of propiverine. The upper limit of the 95% CI in both the FAS and PP analysis set was lower than the non-inferiority margin of 1.0; therefore, it has been shown that propiverine ER 30 mg was non-inferior to tolterodine ER 4 mg (Fig. 4).

Similarity of propiverine ER 30 mg and tolterodine ER 4 mg was also shown for all secondary endpoints (Table 2). The number of urge incontinence episodes per 24 h decreased significantly more in the propiverine group at both control time points, 2 weeks ( $P = 0.026$ ) and 8 weeks ( $P = 0.028$ ). The onset of drug effect was already seen after only 2 weeks of treatment (visit 3) for both substances (13.7 days for propiverine vs 15.4 days for tolterodine;  $P = 0.484$ ). Further improvement for all examined endpoints was recorded after 8 weeks of therapy (Table 2).

The patients' subjective treatment effect was assessed every 2 weeks. For both groups a high early treatment effect after 2 weeks was evident, 71.0% for propiverine ER 30 mg and 68.5% for tolterodine ER 4 mg. Further improvement of the treatment benefit was reported from another 11.1 and 6.2% of patients after 4 weeks of treatment, 4.9 and 3.1% after 6 weeks, and 1.9 and 0% after 8 weeks for the two groups, respectively (Fig. 5); thus, altogether 88.9% of patients treated with propiverine ER compared with 77.8% treated with

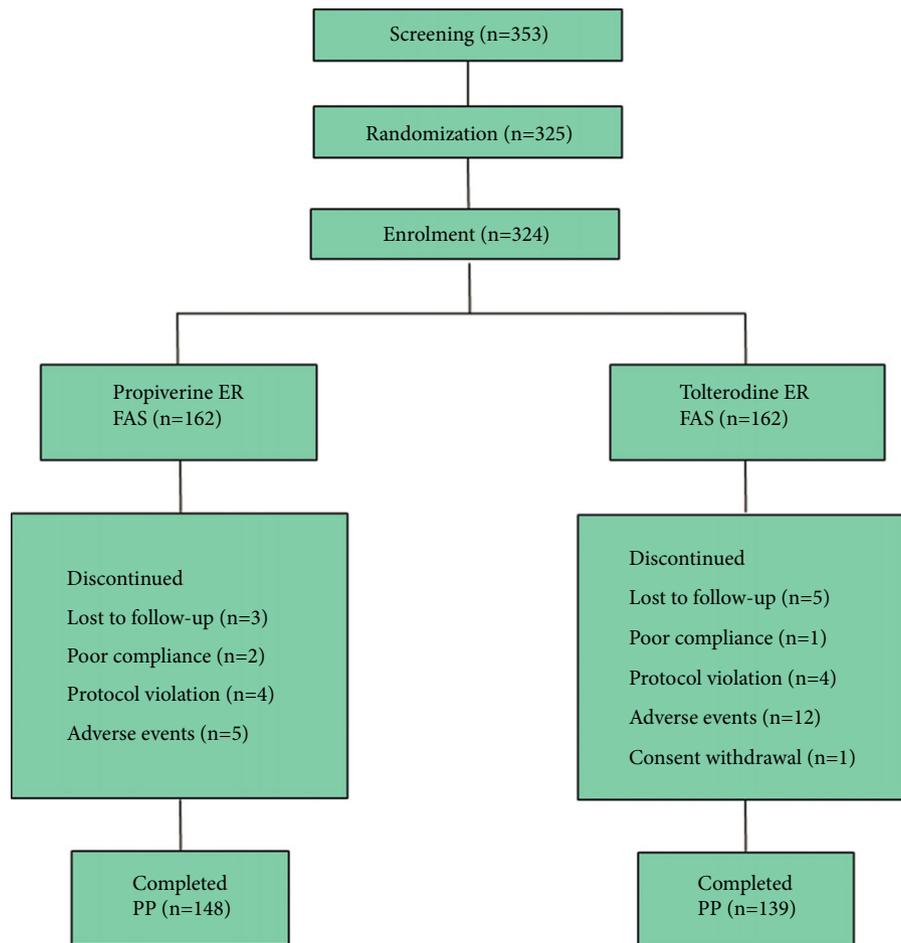
tolterodine ER ( $P = 0.007$ ) reported a benefit from antimuscarinic therapy in the patients' self-assessment after 8 weeks.

Even though more patients in the propiverine ER 30 mg treatment group reported a benefit from therapy, the subjective benefit levels assessed as 'large' or 'small' were similar in the two groups: 68.1% of the propiverine ER 30 mg vs 67.5% of the tolterodine ER 4 mg group assessed the overall benefit as large and 31.9 vs 32.5% as small, respectively ( $P = 0.92$ ).

### Safety and Tolerability

The tolerability of propiverine ER 30 mg and tolterodine ER 4 mg was good during the entire treatment period with a similar rate of adverse events (45.1% under propiverine ER 30 mg vs 42.0% under tolterodine ER 4 mg;  $P = 0.575$ ). The frequency of all reported adverse drug reactions is summarized in Table 3. The severity of these adverse drug reactions was generally mild in both treatment groups. Four serious adverse events were recorded in four patients (2.5%; all in the tolterodine ER treatment group), but were assessed without relation to study medication intake. The discontinuation rate attributable to adverse events was greater under tolterodine ER 4 mg (7.4%) compared with propiverine ER 30 mg (3.1%).

All safety-relevant measures (laboratory test results, vital signs, 12-lead ECGs and abdominal ultrasonography) showed no abnormal results after 8 weeks of propiverine ER 30 mg or tolterodine ER 4 mg treatment.

**Fig. 2** Patient disposition. ER, extended release; FAS, full analysis set; PP, per protocol.

## Discussion

The present study compared the efficacy and safety of propiverine ER 30 mg with tolterodine ER 4 mg in the treatment of Chinese patients with OAB. For propiverine ER 30 mg, an early onset of a treatment effect is known from previous studies for all age groups [23,29] and could be reconfirmed with an onset of efficacy after only 2 weeks of therapy, whereby the treatment effect was even slightly earlier in the propiverine group ( $P = 0.48$ ; Table 2).

The primary objective, demonstration of non-inferiority of propiverine ER 30 mg in comparison to tolterodine ER 4 mg for the change from baseline in the voiding frequency per 24 h after 8 weeks of treatment, was achieved. Propiverine ER 30 mg was even significantly more effective than tolterodine ER 4 mg in terms of decreasing the voiding frequency per 24 h ( $-4.6$  vs  $-3.8$ ;  $P = 0.005$ ) and the mean number of incontinence episodes per 24 h ( $-0.9$  vs  $-0.3$ ;  $P = 0.027$ ).

The benefit of treatment as deriving from the patient's self-assessment increased over time. More than two-thirds of

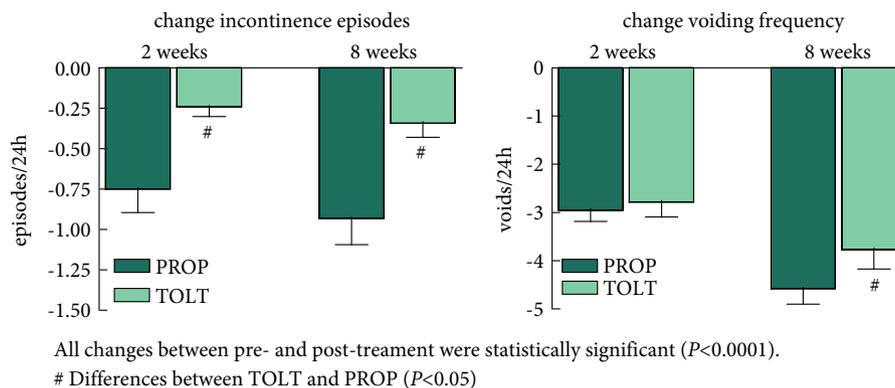
patients reported an improvement of their OAB symptoms after 2 weeks of treatment increasing to 77.8 and 88.9% of patients after 8 weeks of treatment for tolterodine ER 4 mg and propiverine ER 30 mg, respectively ( $P = 0.007$ ). As shown in Fig. 5, a treatment effect for both antimuscarinics as assessed by the patients themselves was very high after the first 4 weeks of treatment. If patients respond to an antimuscarinic therapy, the therapeutic effect can be expected within the first month of treatment. In contrast, the level of the treatment benefit increased remarkably within time. After 8 weeks of therapy, an additional 54 patients (33.3%; propiverine ER 30 mg) and 33 patients (20.4%; tolterodine ER 4 mg) assessed their treatment benefit as large. This improvement in the degree of benefit was not dependent on the overall duration of treatment.

The clinical efficacy results for propiverine ER were similar to those of previously published studies. For instance, when comparing the efficacy improvements from the propiverine ER 30 mg group in this study ( $n = 162$ ) with the results for the propiverine ER group ( $n = 372$ ) from the placebo and comparator-controlled clinical trial performed in Europe [23],

**Table 2** Efficacy endpoint results (full analysis set).

Efficacy variables	Propiverine ER 30 mg (N = 162)	Tolterodine ER 4 mg (N = 162)	P
Mean (SD) of voidings/24 h*			
Baseline	15.2 (5.8)	14.7 (6.0)	0.2132
2 weeks	12.2 (4.8)	11.9 (4.9)	0.2413
Change from baseline to 2 weeks	-3.0 (3.0)	-2.8 (4.0)	0.1781
8 weeks (end of treatment)	10.6 (4.5)	10.9 (4.8)	0.6295
<b>Change from baseline to end of treatment</b>	<b>-4.6 (4.1)</b>	<b>-3.8 (5.1)</b>	<b>0.0050</b>
Mean (SD) voided volume, mL*			
Baseline	98.9 (43.1)	106.1 (39.5)	0.1216
2 weeks	125.8 (57.7)	133.9 (57.8)	0.1583
Change from baseline to 2 weeks	26.9 (36.2)	27.8 (42.3)	0.9206
8 weeks (end of treatment)	140.2 (61.7)	147.4 (64.1)	0.9206
Change from baseline to end of treatment	41.3 (48.3)	41.3 (54.5)	0.8887
Mean (SD) urgency incontinence episodes/24 h*			
Baseline	1.3 (3.1)	0.6 (1.6)	0.2251
2 weeks	0.5 (2.2)	0.4 (1.3)	0.5667
Change from baseline to 2 weeks	-0.8 (1.8)	-0.2 (0.8)	0.0264
8 weeks (end of treatment)	0.3 (1.6)	0.3 (1.1)	0.7180
<b>Change from baseline to end of treatment</b>	<b>-0.9 (2.1)</b>	<b>-0.3 (1.1)</b>	<b>0.0275</b>
Time of onset of drug effect, days <sup>†</sup>			
Mean (SD)	13.7 (1.1)	15.4 (1.4)	0.4841
<b>Benefit from treatment (patient's self-assessment)<sup>‡</sup></b>			
2 weeks			
No, n (%)	47 (29.0)	51 (31.5)	0.6285
Yes, n (%)	115 (71.0)	111 (68.5)	
8 weeks			
No, n (%)	18 (11.1)	36 (22.2)	0.0073
Yes, n (%)	144 (88.9)	126 (77.8)	

ER, extended release. \*Wilcoxon's test; <sup>†</sup>log-rank test; <sup>‡</sup>Fisher's exact test. In case of missing values, the last observation carried forward was applied for the full analysis set.

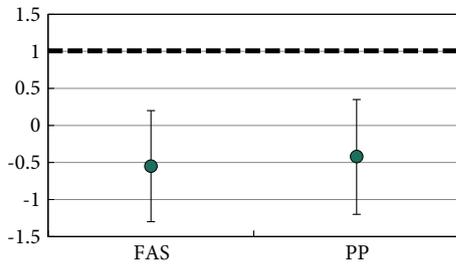
**Fig. 3** Changes from baseline in the mean number of incontinence episodes/24 h and the mean voiding frequency/24 h after 2 and 8 weeks of treatment with propiverine (PROP) extended release (ER) 30 mg and tolterodine (TOLT) ER 4 mg (full analysis set).

the percentage changes from baseline in the mean number of voidings per 24 h were similar (-30.2 and -28.6%, respectively). For the mean number of incontinence episodes, an improvement was reached by 73.8 and 73.1% of patients in the present study and the European trial, respectively, even though the inclusion criteria differed because patients in the present study had not necessarily to present urge incontinence at baseline as had been required in the earlier study. Although the mean voided volume at baseline differed for both studies, the mean voided volume improved by 41.3

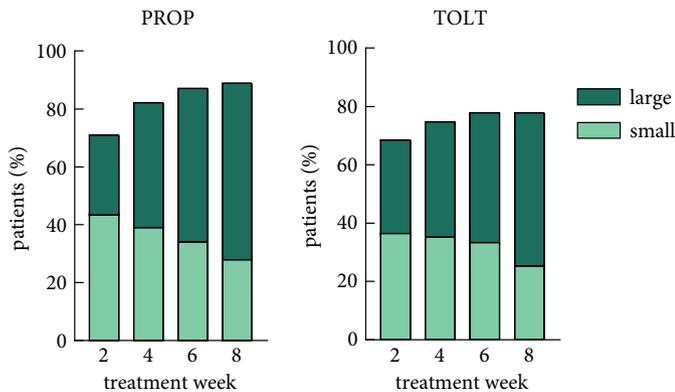
mL and 40.1 mL, respectively. In conclusion, the main efficacy variables were similar in the different ethnic groups, even though the demographic data differed slightly because the patient population in the present study was ~5 years younger and comprised a smaller female population (74.7 vs 89% females).

A limitation of the present study design was the overall treatment duration of only 8 weeks, although the full treatment effect of propiverine ER or tolterodine ER when

**Fig. 4** Difference (tolterodine - propiverine) of change of mean number of voidings/24 h at 8 weeks of treatment vs baseline in relationship to non-inferiority margin. FAS, full analysis set; PP, per protocol.



**Fig. 5** Patients self-reported small or large benefit from treatment after 2, 4, 6 and 8 weeks of treatment with propiverine (PROP) extended release (ER) 30 mg and tolterodine (TOLT) ER 4 mg (full analysis set).



compared with other long-term data [24,26,30–32] is fully pronounced at this time. Since the marketing authorization of propiverine ER 30 mg in several European countries, four non-interventional studies were performed over a treatment duration of 12 weeks in the outpatient setting. In three of the four non-interventional studies the effectiveness and safety

were determined in 5565 female and male patients with OAB [24], in 2219 men with OAB and benign prostatic syndrome [26], and in 1335 female and male patients with flexible propiverine ER doses containing 30 or 45 mg [33]. The improvement with respect to the percentage changes from baseline in the mean number of voidings per 24 h were 30.8, 31.4 and 30.3% after 4 weeks of treatment, increasing to 40.8, 42.3 and 39.8% after 12 weeks for the three non-interventional studies, respectively. These results confirm on the one hand the efficacy of propiverine ER 30 mg over a treatment period of 12 weeks and on the other hand a similar treatment effect with controlled trials conducted over 4–8 weeks. Moreover, the data support the good effectiveness and tolerability of propiverine ER 30 mg under real-life conditions.

Oelke et al. [34] analysed the influence of propiverine ER 30 mg on quality of life (patient perception of bladder condition) and cognitive function in 201 patients with OAB aged ≥70 years. Folstein’s Mini Mental State Examination (MMSE) test was additionally used to assess cognitive function. After 12 weeks of treatment with propiverine ER 30 mg, the quality of life improved and no signs of cognitive alteration were observed, not even in patients with previously diagnosed mild cognitive impairment.

Even though a different propiverine dose was applied, three randomized controlled studies over 12 weeks’ treatment duration have been performed comparing propiverine IR 20 mg with placebo and active control (solifenacin, imidafenacin). For all micturition diary variables, propiverine IR 20 mg was superior to placebo and similar to imidafenacin and solifenacin [21,27,28].

Another point for discussion with regard to the present clinical trial is the lack of a placebo group. The superiority of propiverine and tolterodine over placebo, however, is well known from numerous other studies [21,22,27,28,

**Table 3** Main adverse drug reactions (safety population).

Adverse reaction, n (%)	Propiverine ER 30 mg (N = 162)	Tolterodine ER 4 mg (N = 162)
Overall	66 (40.7)	64 (39.5)
Discontinuation because of adverse events	5 (3.1)	12 (7.4)
Dry mouth	45 (27.8)	43 (26.5)
mild/moderate/severe	40 (24.7)/4 (2.5)/1 (0.6)	38 (23.5)/3 (1.9)/2 (1.2)
Dysuria	10 (6.2)	14 (8.6)
mild/moderate/severe	8 (4.9)/2 (1.2)/0	13 (8.0)/1 (0.6)/0
Constipation	5 (3.1)	2 (1.2)
Mild/moderate/severe	2 (1.2)/3 (1.9)/0	2 (1.2)/0/0
Dry eye	4 (2.5)	1 (0.6)
mild/moderate/severe	3 (1.9)/1 (0.6)/0	0/1 (0.6)/0
Palpitation/chest depression	2 (1.2)	4 (2.5)
mild/moderate/severe	1 (0.6)/1 (0.6)/0	0/4 (2.5)/0
Blurred vision	0 (0.0)	2 (1.2)
Mild/moderate/severe	0/0/0	2 (1.2)/0/0

ER, extended release.

30–32,35,36] and underlined in meta-analyses for antimuscarinics [35,36].

The analysis of the baseline demographic data shows that the average age of the patient population was 50 years, ~8 years younger when compared with the mean age (58 years) of all reported clinical trials from the meta-analysis by Buser *et al.* [35]. Of the patients in that study, only 11% were previously treated with antimuscarinics or other related OAB therapies, highlighting the need for increased region-wide care of patients with OAB symptoms. The gender distribution of ~25% of males and 75% females was similar to that in the current literature although several publications only reported the data on female patients [35].

Tolerability, as recorded in the present clinical trial, confirms the safe application of propiverine ER 30 mg for the treatment of OAB, which has been available in several European countries for ~10 years. Altogether, adverse drug reactions were reported in 130 patients; 66 (40.7%) of the propiverine and 64 (39.5%) of the tolterodine group. In these patients, the classic antimuscarinic side effects were evenly distributed between groups. As for other antimuscarinics, the most frequently reported adverse drug reaction was dry mouth (27.8% with propiverine ER and 26.5% with tolterodine ER; in 89% of patients this was of mild intensity), followed some distance away by dysuria and constipation. By contrast, accommodation disorders were recorded less frequently in this study population (Table 3).

Treatment compliance was high: 91.4% of the patients in the propiverine group and 85.8% of the patients in the tolterodine group completed the 8 weeks' intake of study medication, and only 3.1 and 7.4% of patients, respectively, dropped out of the study prematurely because of adverse events. Five patients in the propiverine group discontinued treatment, in four cases because of adverse drug reactions related to antimuscarinic treatment of mild to moderate intensity and in one case as a result of a mild unrelated adverse event (oedema of the lower extremities). In the tolterodine group, eight of the 12 patients discontinued treatment because of related adverse drug reactions of mild to severe intensity and four patients because of serious adverse events that were not related to antimuscarinic treatment (bladder tumour, pneumonia, anembryonic gestation, cerebral reinfarction). Taking all adverse drug reactions together, 81.3% were of mild, 15.8% of moderate and 2.9% of severe intensity.

The overall safety assessment included laboratory examinations, ECGs and ultrasonography of the abdominal/urological region. Neither pathological findings nor changes with respect to the baseline examination were recorded. In only one tolterodine-treated patient, the ECG control recorded an abnormal change in the T-wave. Additionally, mild palpitations were recorded in five patients (3.1%) in

the tolterodine ER group and one (0.6%) patient in the propiverine ER group. These results are consistent with routine ECG controls used in previous clinical trials conducted with propiverine [22,23,25,27,28]. Only one controlled clinical trial conducted with a propiverine IR 20 mg formulation in Japan described a prolonged but within the norm QTc interval (<500 ms) and a slightly elevated pulse rate for propiverine, not taking into account the numerous factors influencing the validity and interpretation of these results. Notwithstanding the above, the authors also concluded that the pro-arrhythmic risk in both the imidafenacin and propiverine group were inconclusive and that the ECG results were within the biological variability, i.e. will be without any clinical concern [21].

Additionally, two propiverine studies within special risk groups (elderly and postmenopausal women) and another study in male patients with coronary heart disease were performed in white populations [37,38]. In all three studies, the ECG variables were not affected by propiverine when compared with placebo, i.e. no QTc prolongation, QTc dispersion or T-wave changes during rest and exercise were recorded. The results of these clinical studies substantiate previous basic research on the effect of propiverine with respect to the potential duration of action in ventricular myocytes of guinea pigs, in human ventricular tissue biopsies, and in dog Purkinje fibres. All these *in vitro* examinations showed no evidence for an enhanced cardiovascular safety risk [39].

Altogether, the adverse reaction profile observed in this clinical trial did not differ in the Chinese patient population when compared with previous reports on propiverine in Europe.

In conclusion, the results of this randomized controlled non-inferiority trial confirmed that propiverine ER 30 mg was at least as effective and safe as tolterodine ER 4 mg for the treatment of patients with OAB. Moreover, the results were in line with previously published propiverine data throughout Europe and Japan. With respect to the change in the voiding frequency per 24 h, the primary efficacy outcome variable, and the change in urgency incontinence episodes, propiverine ER 30 mg was more effective than tolterodine ER 4 mg.

## Acknowledgements

This clinical trial was sponsored by Lee's Pharmaceutical Ltd, Hong Kong and supported with a grant by APOGEPHA Arzneimittel GmbH, Dresden, Germany.

Editorial assistance was provided by Cornelia Feustel, consultant of APOGEPHA Arzneimittel GmbH and Sophie Liang, employee of Lee's Pharmaceutical Limited.

## Conflict of Interest

Cornelia Feustel reports consultancy for APOGEPHA Arzneimittel GmbH, Dresden, Germany.

## References

- Stewart WF, Van Rooyen JB, Cundiff GW et al. Prevalence and burden of overactive bladder in the United States. *World J Urol* 2003; 20: 327–36
- Temml C, Heidler S, Ponholzer A, Madersbacher S. Prevalence of the overactive bladder syndrome by applying the International Continence Society definition. *Eur Urol* 2005; 48: 622–7
- Cheung WW, Blank W, Borawski D, Tran W, Bluth MH. Prevalence of overactive bladder, its under-diagnosis, and risk factors in a male urologic veterans population. *Int J Med Sci* 2010; 7: 391–4
- Zhang W, Song Y, He X, Huang H, Xu B, Song J. Prevalence and risk factors of overactive bladder syndrome in Fuzhou Chinese women. *Neurourol Urodyn* 2006; 25: 717–21
- Jo JK, Lee S, Kim YT et al. Analysis of the risk factors for overactive bladder on the basis of a survey in the community. *Korean J Urol* 2012; 53: 541–6
- Milsom I, Stewart W, Thüroff JW. The prevalence of overactive bladder. *Am J Manag Care* 2000; 6: S565–73
- Sang JH, Park HM. Survey on the prevalence of overactive bladder in healthy Korean postmenopausal women. *J Korean Soc Menopause* 2012; 18: 60–6
- Tikkinen KAO, Tammela TLJ, Rissanen AM, Valpas A, Huhtala H, Auvinen A. Is the prevalence of overactive bladder overestimated? A population-based study in Finland. *PLoS One* 2007; 2: e195
- Chen GD, Lin TL, Hu SW, Chen YC, Lin LY. Prevalence and correlation of urinary incontinence and overactive bladder in Taiwanese women. *Neurourol Urodyn* 2003; 22: 109–17
- Milsom I, Abrams P, Cardozo L, Roberts RG, Thüroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU Int* 2001; 87: 760–6
- Wang Y, Xu K, Hu H et al. Prevalence, risk factors, and impact on health related quality of life of overactive bladder in China. *Neurourol Urodyn* 2011; 30: 1448–55
- Wen JG, Li JS, Wang ZM et al. The prevalence and risk factors of OAB in middle-aged and old people in China. *Neurourol Urodyn* 2014; 33: 387–91
- Abrams P, Cardozo L, Fall M et al. The standardisation of terminology of lower urinary tract function: report from the standardisation sub-committee of the international continence society. *Neurourol Urodyn* 2002; 21: 167–78
- Zhang L, Zhu L, Xu T et al. A population-based survey of the prevalence, potential risk factors, and symptom-specific bother of lower urinary tract symptoms in adults Chinese women. *Eur Urol* 2015; 68: 97–112
- May K, Giessmann T, Wegner D et al. Oral absorption of propiverine solution and of the immediate and extended release dosage forms: influence of regioselective intestinal elimination. *Eur J Clin Pharmacol* 2008; 64: 1085–92
- Huang M, Tian Y, Zhang Z, Zhang H, Lin H. Determination of propiverine hydrochloride in human plasma by high performance liquid chromatography-tandem mass spectrometry: application to the pharmacokinetic study of a sustained release formulation. *Arzneim Forsch/Drug Res* 2011; 61: 494–501
- Siegmund W, Siegert J, Richter K, Schnabel F, Feustel C, Kirch W. Influence of a fat-rich meal on bioavailability of extended-release and immediate-release propiverine. *J Clin Pharmacol* 2012; 52: 681–90
- McKeage K. Propiverine: a review of its use in the treatment of adults and children with overactive bladder associated with idiopathic or neurogenic detrusor overactivity, and in men with lower urinary tract symptoms. *Clin Drug Investig* 2013; 33: 71–91
- Wuest M, Christ T, Hiller N, Braeter M, Ravens U. Effects of three metabolites of propiverine on voltage-dependent L-type calcium currents in human atrial myocytes. *Eur J Pharmacol* 2008; 598: 94–7
- Wuest M, Hecht J, Christ T et al. Pharmacodynamics of propiverine and three of its main metabolites on detrusor contraction. *Br J Pharmacol* 2005; 145: 608–19
- Homma Y, Yamaguchi O. A randomized, double-blind, placebo- and propiverine-controlled trial of the novel antimuscarinic agent imidafenacin in Japanese patients with overactive bladder. *Int J Urol* 2009; 16: 499–506
- Junemann KP, Halaska M, Rittstein T et al. Propiverine versus tolterodine: efficacy and tolerability in patients with overactive bladder. *Eur Urol* 2005; 48: 478–82
- Junemann KP, Hessdorfer E, Unamba-Oparah I et al. Propiverine hydrochloride immediate and extended release: comparison of efficacy and tolerability in patients with overactive bladder. *Urol Int* 2006; 77: 334–9
- Kessler-Zumpe PL, Murgas S, Neumann G, Richter AE. Therapy of overactive bladder with propiverine ER: results of a non-interventional study with a propiverine retard formulation and comparison to clinical studies. *Urologe A* 2009; 48: 1346–51
- Madersbacher H, Halaška M, Voigt R, Alloussi S, Höfner K. A placebo-controlled, multicentre study comparing the tolerability and efficacy of propiverine and oxybutynin in patients with urgency and urge incontinence. *BJU Int* 1999; 84: 646–51
- Oelke M, Murgas S, Baumann I, Schnabel F, Michel M. Efficacy of propiverine ER with or without  $\alpha$ -blockers related to maximum urinary flow rate in adult men with OAB: results of a 12-week, multicenter, non-interventional study. *World J Urol* 2011; 29: 217–23
- Yamaguchi O, Marui E, Kakizaki H et al. Randomized, double-blind, placebo- and propiverine-controlled trial of the once-daily antimuscarinic agent solifenacin in Japanese patients with overactive bladder. *BJU Int* 2007; 100: 579–87
- Gotoh M, Yokoyama O, Nishizawa O. Propiverine hydrochloride in Japanese patients with overactive bladder: a randomized, double-blind, placebo-controlled trial. *Int J Urol* 2011; 18: 365–73
- Siegmund W, Sillén U, Läckgren G, Schnabel F, Mürtz G, Feustel C. Pharmacokinetics and pharmacodynamics of propiverine in children aged between 5 and 10 years with symptoms of overactive bladder. *Clin Pharmacokinet* 2010; 49: 335–42
- Herschorn S, Swift S, Guan Z et al. Comparison of fesoterodine and tolterodine extended release for the treatment of overactive bladder: a head-to-head placebo-controlled trial. *BJU Int* 2010; 105: 58–66
- Landis JR, Kaplan S, Swift S, Versi E. Efficacy of antimuscarinic therapy for overactive bladder with varying degrees of incontinence severity. *J Urol* 2004; 171: 752–6
- van Kerrebroeck P, Kreder K, Jonas U, Zinner N, Wein A. Tolterodine once-daily: superior efficacy and tolerability in the treatment of the overactive bladder. *Urology* 2001; 57: 414–21
- Eisenhardt A, Schneider T, Murgas S, Oelke M. Propiverine ER and Effects of Flexible-Dosing in 1335 Patients with OAB: Results of a Non-Interventional Study. 44th Annual Meeting of the International Continence Society, 2014 Rio de Janeiro, Abstract-No. 585
- Oelke M, Murgas S, Schneider T, Hessdorfer E. Influence of propiverine ER 30 mg once daily on cognitive function in elderly female and male patients with overactive bladder: a non-interventional study to assess real life data. Annual Meeting of the ICS, Barcelona, Spain, 2013. *Neurourol Urodyn* 2013; 32: 800–2

- 35 Buser N, Ivic S, Kessler TM, Kessels AG, Bachmann LM. Efficacy and adverse events of antimuscarinics for treating overactive bladder: network meta-analyses. *Eur Urol* 2012; 62: 1040–60
- 36 Chapple CR, Rechberger T, Al Shukri S et al. Randomized, double-blind placebo- and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder. *BJU Int* 2004; 93: 303–10
- 37 Donath F, Braeter M, Feustel C. The influence of propiverine hydrochloride on cardiac repolarization in healthy women and cardiac male patients. *Int J Clin Pharmacol Ther* 2011; 49: 353–65
- 38 Dorschner W, Stolzenburg JU, Griebenow R et al. Efficacy and cardiac safety of propiverine in elderly patients - A double-blind, placebo-controlled clinical study. *Eur Urol* 2000; 37: 702–8
- 39 Christ T, Wettwer E, Wuest M et al. Electrophysiological profile of propiverine - relationship to cardiac risk. *Naunyn Schmiedebergs Arch Pharmacol* 2007; 376: 431–40

**Correspondence:** Cornelia Feustel, Consultant for APOGEPHA Arzneimittel GmbH, Kyffhäuserstraße 27, 01309 Dresden, Germany.

**e-mail:** co-feustel@t-online.de

**Abbreviations:** ER, extended release; OAB, overactive bladder; FAS, full analysis set; IR, immediate release; ECG, electrocardiogram; PP, per protocol.