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Tamsulosin Oral Controlled Absorption System (OCAS) in Patients with Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia (LUTS/BPH): Efficacy and Tolerability in a Phase 2b Dose-Response Study

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Abstract

Objectives: This phase 2b randomised, placebo-controlled trial (RCT) was a dose-response study to assess the efficacy and safety of three different doses of a new formulation of tamsulosin (the oral controlled absorption system: OCAS) and to determine which dose(s) should be further evaluated in a phase 3a RCT.

Methods: After a two-week single-blind, placebo run-in period, older men (≥45 years) with lower urinary tract symptoms (LUTS: total International Prostate Symptom Score (I-PSS) ≥13) suggestive of benign prostatic hyperplasia (BPH: maximum flow rate 4–12 ml/s) were randomised to 12 weeks of treatment with placebo or tamsulosin OCAS 0.4, 0.8 or 1.2 mg once daily. The primary efficacy variable was the mean change from baseline to endpoint in total I-PSS. Tolerability was mainly assessed by documenting adverse events (AEs) reported by the patient.

Results: A total of 839 patients were randomised to placebo ($N = 213$) or tamsulosin OCAS 0.4 mg ($N = 206$), 0.8 mg ($N = 209$) or 1.2 mg ($N = 211$). At endpoint, all three tamsulosin OCAS doses reduced the total I-PSS to a significantly greater extent than placebo (6.0 points or 34.5%). There were no clinically relevant differences between 0.4 mg (7.6 points or 42.4%), 0.8 mg (8.1 points or 46.6%) or 1.2 mg (8.2 points or 45.2%). The same applied for the improvement in the patient's urinary condition, both in the opinion of the patients and investigators. The incidence of AEs increased with increasing tamsulosin OCAS dose and was highest with the 1.2 mg dose. The two most frequently reported AEs were those commonly associated with α_1-adrenoceptor antagonists: dizziness and abnormal ejaculation. The incidence of dizziness was comparable for the 0.4 mg dose (0.5%) and placebo (1.4%) but higher with 0.8 and 1.2 mg (5.8% and 4.3%, respectively). The incidence of abnormal ejaculation was only marginally higher with 0.4 mg (2.0%) than placebo (0.9%) and showed a clear dose-response relationship with the higher doses of 0.8 mg (4.4%) and 1.2 mg (8.1%).

Conclusions: All three tamsulosin OCAS doses tested were effective in relieving urinary symptoms and improving disease-specific quality of life in LUTS/BPH patients. The 0.8 mg and, in particular, the 0.4 mg doses were better tolerated than the 1.2 mg dose. Therefore, these two doses were selected for further evaluation in a phase 3a placebo- and comparator (tamsulosin modified release capsules) controlled trial.

Keywords: Tamsulosin; Oral controlled absorption system; Efficacy; Tolerability; Placebo; Randomised controlled trial

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1. Introduction

Lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) are common in older men. In epidemiological community-based surveys, approximately 25% of men aged 40 years and over indicate to have LUTS [1–3]. Pharmacological therapy is the first treatment choice in many patients of which α_1-adrenoceptor (AR) antagonists are the most frequently prescribed [3]. Based on the existing literature including the Medical Therapy Of Prostatic Symptoms (MTOPS) trial results it is now frequently recommended that one should use α_1-AR antagonist monotherapy in the majority of LUTS/BPH patients at the outset and add a 5α-reductase inhibitor such as finasteride or dutasteride in patients at high risk of progression, i.e. patients with a large prostate volume (e.g. >40 ml) or a high prostate specific antigen (PSA) [4].

Of the currently clinically available α_1-AR antagonists (alfuzosin, doxazosin, prazosin, tamsulosin, terazosin), tamsulosin modified release (MR) 0.4 mg once daily capsule has the most favourable tolerability/efficacy ratio [5–7] and is the agent most frequently used in clinical practice. This is probably due to this agent's beneficial effects in relieving LUTS with minimal undesired effects on the cardiovascular system. This apparent uroselectivity of action is suggested to be related to a number of factors including tamsulosin's greater selectivity for subtypes present and/or functional in the LUT (i.e. α_{1A} and α_{1D}-ARs) over those in the blood vessels (i.e. α_{1B}-ARs, in particular in the elderly), its selective distribution to prostatic tissue as compared to the plasma and its MR formulation [7]. The tamsulosin oral controlled absorption system (OCAS) was developed to improve the pharmacokinetic profile of the existing tamsulosin MR formulation. The goals were 3-fold: it should provide (1) a lower maximum plasma concentration (C_{max}), (2) a more constant release of tamsulosin over 24 hours and (3) independence of the pharmacokinetics on food intake, thereby providing a better efficacy/safety ratio [8,9]. The OCAS technology is a controlled release system of a gel matrix type that rapidly hydrates and is maintained in this hydrated state in the colon. The gel matrix then has sufficient strength to achieve drug release in the colon where water is poorly available [10]. It is this feature of the OCAS formulation that results in more constant delivery of tamsulosin over 24 hours [9]. Results from phase I studies in healthy young subjects show that tamsulosin OCAS indeed has more pronounced slow release characteristics compared to the MR formulation (under fed conditions) with a lower C_{max} and with a more constant 24-hour plasma concentration [9]. This is maintained when tamsulosin OCAS is administered with or without food/on an empty stomach [9]. The present paper describes the results of a randomised, double-blind, placebo-controlled dose-response phase 2b study with tamsulosin OCAS.

2. Materials and methods

This study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by institutional review boards and/or independent ethics committees.

2.1. Study design

This was a double-blind, randomised, placebo-controlled, parallel group, multi-national (15 countries), multi-centre (77 European centres) dose-response study of three tamsulosin OCAS doses (0.4 mg, 0.8 mg and 1.2 mg tablets once daily) in patients with LUTS/BPH. After a 2-week, single-blind placebo run-in period, patients were randomised to 12 weeks of double-blind treatment with placebo or one of the three tamsulosin OCAS tablets once daily. The patients who were randomised to tamsulosin OCAS 1.2 mg received 0.8 mg tablets during the first 2 weeks and 1.2 mg tablets during the remaining 10 weeks. Tamsulosin OCAS was administered in the morning, with or without food. During the 12-week treatment period, patients visited the clinic after 2, 4, 8 and 12 weeks.

2.2. Study population (inclusion and exclusion criteria)

Men aged 45 years or over with voiding (''obstructive'') and storage (''irritative/filling'') symptoms diagnosed as LUTS/BPH with a total International Prostate Symptom Score (I–PSS) ≥13 (at the enrolment and randomisation visit) and a maximum flow rate (Q_{max}) ≥4 ml/s and ≤12 ml/s (for a voided volume ≥120 ml) during free flow studies were suitable for enrolment into the study if they had given informed consent. The exclusion criteria were those usually applied in LUTS/BPH clinical trials with α_1-AR antagonists. These included any other urological procedures or conditions which may cause LUTS (e.g. previous surgery to the LUT or pelvic region, neurological bladder disorders, bladder neck stenosis, stone in the bladder or urethra, recurrent urinary tract infections, bladder or prostate cancer, urethral stricture). Patients with hepatic or renal insufficiency, clinically significant cardiovascular or cerebrovascular diseases within six months prior to enrolment (e.g. uncontrolled angina, myocardial infarction, heart failure (NYHA class III–IV), stroke, orthostatic hypotension or significant ventricular arrhythmias), central nervous system conditions (e.g. senile dementia, multiple sclerosis, Parkinson's disease and psychiatric disorders) or life-threatening diseases were excluded. Finally, patients who were taking or had taken other drugs for LUTS/BPH (i.e. 5α-reductase inhibitors within three months and α_1-AR antagonists and plant extracts within one month prior to enrolment), were hypersensitive to α_1-AR antagonists or their excipients, were taking drugs which could interfere with the pharmacodynamics of tamsulosin OCAS (e.g. other α-AR antagonists, α-AR agonists, α/β-AR antagonists, cholinergics or anti-cholinergics) or were taking or had been taken other investigational drugs within the previous three months were excluded from enrolment.

2.3. Assessment of efficacy

Efficacy was assessed at all visits by means of the I-PSS questionnaire [11]. The patient had to rate the frequency of seven urinary symptoms (four related to voiding and three related to storage symptoms) on a scale from 0–5 with a total score range from 0–35. In addition, they had to indicate how they would feel if they were to spend the rest of their life with the urinary condition as it was at the time of completing the questionnaire using the I-PSS disease-specific quality of life (QoL) single question to be rated from 0–6 (also referred to as the bother score).

The mean change from baseline to endpoint in total I-PSS was the primary efficacy variable. The endpoint visit was defined as the last post-baseline assessment during double-blind treatment for which efficacy evaluations were available. At the end of the study, the investigator had to provide a global assessment of their interpretation of treatment outcome: worsened, unchanged, slightly improved or much improved.

2.4. Assessment of safety/tolerability

Tolerability was assessed by asking the patient at every visit whether he had experienced any untoward medical occurrence, whether or not considered to be related to the study medication. If these occurred for the first time or worsened in intensity after start of double-blind treatment or a relationship to study medication had arisen, they were defined as treatment-emergent adverse events (TEAEs). The intensity (mild, moderate, severe) and relationship to study medication (possibly, probably or unlikely related) were also documented. In addition, vital signs (supine and standing blood pressure and pulse rate) were measured at each visit. A 12-lead electrocardiogram (ECG), laboratory evaluations and physical examination were performed at the enrolment and final visit (and laboratory evaluations after 2 weeks of double-blind treatment).

2.5. Statistical methods and sample size

In order to detect a 2-point difference between tamsulosin OCAS and placebo in mean total I-PSS reduction from baseline to endpoint with a 2-sided $\alpha = 0.05$ and a power of 80% and taken into account a 10–15% drop-out rate both prior to and after randomisation, at least 760 patients were to be enrolled and at least 640 patients (160 patients per treatment group) to be randomised.

Changes in I-PSS questionnaire variables were subjected to analysis of variance (ANOVA) including the model factors centre and treatment. A hierarchical testing procedure (step-down, starting with the comparison of the highest dose against placebo) was followed eliminating the need for adjustment of statistical significance levels to account for the multiple comparisons between treatments. The chi-square test was used for the number of responders and the investigator global assessment.

3. Results

3.1. Demographics and other baseline characteristics

A total of 839 patients were randomised to placebo ($N = 213$), tamsulosin OCAS 0.4 mg ($N = 206$), 0.8 mg ($N = 209$) or 1.2 mg ($N = 211$) once daily. The demographics and other baseline characteristics are presented in Table 1. The mean age was approximately 65 years. The mean total I-PSS was around 18 points, the mean Q_{max} 10 ml/s and the mean prostate volume slightly over 40 ml. There were no relevant differences between the treatment groups for any of the baseline characteristics.

The majority of randomised patients completed the study. The discontinuation rate after randomisation was very low (40 patients or 4.8%), with no major differences between the 4 treatment groups (Fig. 1). Discontinuation due to TEAEs was the most frequent reason for withdrawal (19 patients or 2.3%). In addition, 5 patients (0.6%) discontinued due to insufficient response and 16 patients (1.9%) for other reasons (including 6 patients (0.7%) because they were lost to follow-up, 1 patient (0.1%) due to a protocol violation and 9 patients (1.1%) due to other non-specified reasons).

3.2. Efficacy results

All results are presented for the intent-to-treat (ITT) of full analysis set (FAS) population, i.e. all patients who took at least one dose of double-blind medication and provided primary efficacy data at baseline and at least 1 post-baseline visit.

Table 1
Demographics and other baseline characteristics (SAF, except ITT for total I-PSS)

Mean (S.D.) for	Placebo $N = 212$	Tamsulosin OCAS 0.4 mg $N = 203$	Tamsulosin OCAS 0.8 mg $N = 206$	Tamsulosin OCAS 1.2 mg $N = 210$
Age (years)	64.8 (7.9)	65.5 (8.1)	65.3 (8.0)	64.7 (8.2)
Weight (kg)	79.4 (11.8)	80.2 (11.4)	81.0 (11.8)	80.8 (12.5)
Height (cm)	173.2 (7.3)	173.8 (6.9)	174.2 (6.8)	173.9 (6.4)
Total I-PSS	17.8 (4.0)	18.0 (4.3)	17.7 (4.5)	18.2 (4.4)
Q_{max}: ml/s	9.82 (2.04)	9.66 (1.85)	9.70 (1.87)	9.71 (1.80)
Prostate volume: ml	40.9 (18.7)	41.3 (20.9)	41.4 (21.5)	42.9 (20.4)
PSA: ng/ml	2.86 (2.45)	2.48 (2.02)	2.85 (2.63)	3.04 (3.28)

SD: standard deviation; Q_{max} and PSA data at enrolment instead of baseline visit; total I-PSS $N = 210$ for placebo; prostate volume $N = 108$ for tamsulosin OCAS 1.2 mg.

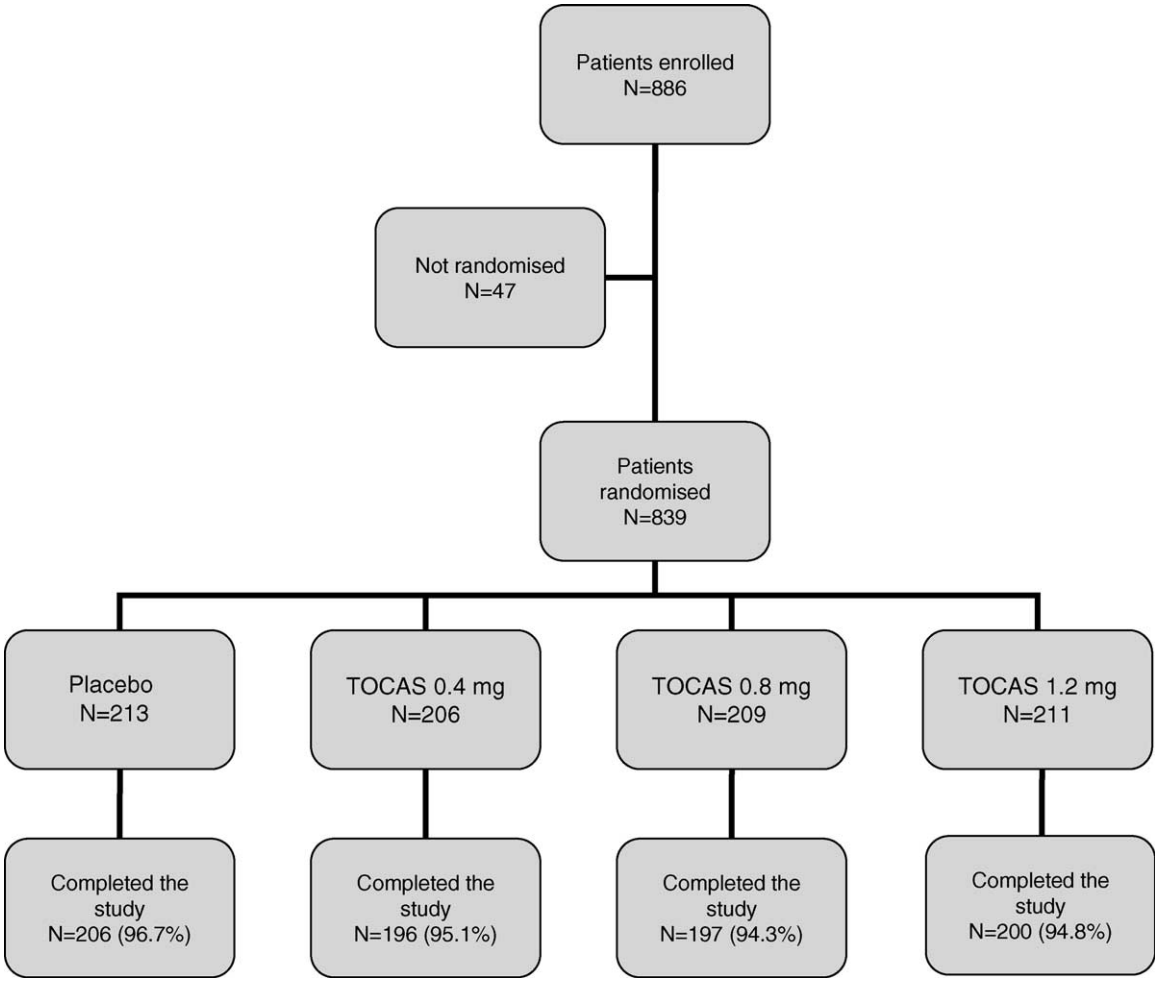

Fig. 1. Flow diagram of the number of patients enrolled, randomised and completing the study per treatment group.

3.2.1. I-PSS questionnaire

The mean change in total I-PSS from baseline to endpoint is shown in Fig. 2. The mean reduction at endpoint was 6.0 (34.5%) with placebo and 7.6 (42.4%), 8.1 (46.6%) and 8.2 (45.2%) with tamsulosin OCAS 0.4, 0.8 and 1.2 mg, respectively. The difference versus placebo of respectively 1.6, 2.1 and 2.2 points

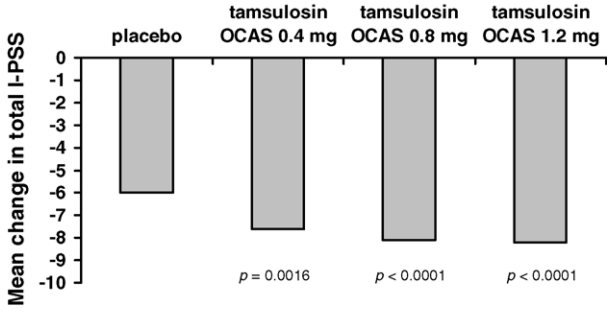

Fig. 2. Mean change in total I-PSS from baseline to endpoint (ITT). *p*-value for mean difference between tamsulosin OCAS and placebo.

was statistically significant for all three tamsulosin OCAS doses. Although the absolute reduction from baseline and the difference versus placebo in the tamsulosin OCAS 0.8 and 1.2 mg groups appeared to be slightly larger than in the 0.4 mg group, the percentage change versus baseline was very comparable in all three tamsulosin OCAS groups (42–47%).

The effect of the different treatments on the total I-PSS over time is visualised in Fig. 3. It appears that all tamsulosin OCAS doses had a fast onset of action. At the first assessment after 2 weeks of treatment, approximately 60% of the total improvement was achieved and 80% of the total improvement was achieved after 4 weeks. It seems that most if not all of the effect was obtained at the last assessment after 12 weeks of treatment.

Patients who had at least a 25% improvement in total I-PSS versus baseline were considered to be responders. At endpoint, 63.0% of patients on placebo compared to 73.4%, 80.1% and 76.7% of patients on

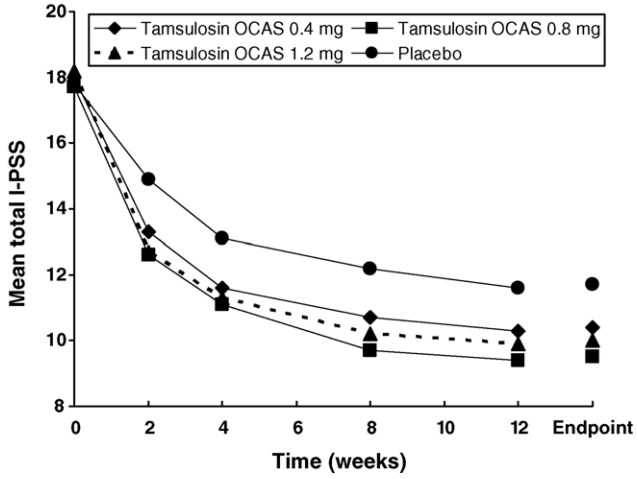

Fig. 3. Effect of treatment on mean total I-PSS over time (ITT).

tamsulosin OCAS 0.4, 0.8 and 1.2 mg, respectively, responded (Table 2). The difference versus placebo was statistically significant for all three doses.

3.2.2. Improvement of the patient's condition

The reduction in urinary symptoms was associated with an improvement in the patients' QoL. The mean change in IPSS-QoL score from baseline to endpoint in the tamsulosin OCAS 0.4 mg (1.3 points; $p = 0.0005$ vs. placebo), 0.8 mg (1.4 points; $p < 0.0001$ vs. placebo) as well as 1.2 mg (1.4 points; $p < 0.0001$ vs. placebo) groups was statistically significantly different from placebo (0.9 points). There were no major differences between the three tamsulosin OCAS groups (Table 2).

Also statistically significantly more patients in the tamsulosin OCAS groups than in the placebo group were assessed by the investigator as improved (85–88% versus 74%; Table 2). This applied in particular for the patients who were considered to be much improved. There were no major differences between the three tamsulosin OCAS dose groups in the percentage of patients believed to be improved: 86% with the 0.4 mg, 88% with the 0.8 mg and 85% with the 1.2 mg dose.

3.3. Safety results

All safety results are presented for the safety population (SAF), i.e. all patients who took at least one dose of double-blind medication and provided post-baseline safety information.

3.3.1. Adverse events

All treatments were very well tolerated. The percentage of patients reporting at least one TEAE was comparable for tamsulosin OCAS 0.4 and 0.8 mg and placebo: 26–30% of patients (Table 3). The incidence was slightly higher with the 1.2 mg dose (36%). Similar results were observed for the percentage of patients indicating to have experienced treatment-related AEs (i.e. possibly or probably related) with a tendency for a slightly higher incidence with the 0.8 mg (13%) and, in particular, 1.2 mg (17%) doses than with the 0.4 mg dose (9%) or placebo (7%).

The most common TEAEs (reported by ≥3.0% of patients in any of the treatment groups) were flu syndrome, infection, dizziness and abnormal ejaculation (Table 3). Whereas the incidence of dizziness was comparable for tamsulosin OCAS 0.4 mg (0.5%) and placebo (1.4%), it was higher with both the 0.8 mg (5.8%) and 1.2 mg (4.3%) doses of tamsulosin OCAS. For abnormal ejaculation, there was a clear dose-response relationship. The percentage of patients with abnormal ejaculation on the 0.4 mg dose was very low (2.0%) and only minimally higher than on placebo (0.9%). However, this increased with the 0.8 mg dose

Table 2
Effect of treatment on other efficacy variables (ITT)

Variable	Placebo $N = 211$	Tamsulosin OCAS 0.4 mg $N = 203$	Tamsulosin OCAS 0.8 mg $N = 206$	Tamsulosin OCAS 1.2 mg $N = 210$
Responders: % of patients[a]	63.0%	73.4%	80.1%	76.7%
(p-value vs. placebo)		0.024	<0.001	0.002
IPSS-QoL: mean (S.D.)				
Baseline	3.7 (1.0)	3.7 (1.0)	3.7 (1.0)	3.8 (1.0)
Change at endpoint	−0.9 (1.3)	−1.3 (1.3)	−1.4 (1.2)	−1.4 (1.2)
Difference vs. placebo		0.4	0.5	0.5
p-value vs. placebo		0.0005	<0.0001	<0.0001
% of patients improved[b]	73.5%	85.7%	88.3%	85.2%
Slightly improved	35.5%	36.9%	34.0%	36.2%
Much improved	37.9%	48.8%	54.4%	49.0%
p-value vs. placebo		0.008	<0.001	0.003

[a] Reduction in total I-PSS from baseline to endpoint ≥25%.
[b] According to the investigator.

Table 3
Treatment-emergent AEs (i.e. COSTART coded terms) reported by ≥3.0% of patients in at least one of the groups (SAF)

N (%) of patients with:	Placebo *N* = 212	Tamsulosin OCAS 0.4 mg *N* = 203	Tamsulosin OCAS 0.8 mg *N* = 206	Tamsulosin OCAS 1.2 mg *N* = 210
At least one TEAE	55 (26%)	58 (29%)	61 (30%)	76 (36%)
Body as a whole	21 (10%)	21 (10%)	24 (12%)	19 (9%)
Flu syndrome	2 (0.9%)	4 (2.0%)	7 (3.4%)	5 (2.4%)
Infection	8 (3.8%)	2 (1.0%)	4 (1.9%)	4 (1.9%)
Nervous system	9 (4.2%)	4 (2.0%)	13 (6.3%)	18 (8.6%)
Dizziness	3 (1.4%)	1 (0.5%)	12 (5.8%)	9 (4.3%)
Urogenital system	8 (3.8%)	10 (4.9%)	12 (5.8%)	24 (11.4%)
Abnormal ejaculation	2 (0.9%)	4 (2.0%)	9 (4.4%)	17 (8.1%)
At least one treatment-related AE	15 (7%)	19 (9%)	27 (13%)	35 (17%)
Nervous system	5 (2.4%)	3 (1.5%)	12 (5.8%)	14 (6.7%)
Dizziness	1 (0.5%)	1 (0.5%)	11 (5.3%)	9 (4.3%)
Urogenital system	5 (2.4%)	6 (3.0%)	9 (4.4%)	18 (8.6%)
Abnormal ejaculation	2 (0.9%)	4 (2.0%)	9 (4.4%)	17 (8.1%)

Table 4
Effect of treatment on standing vital signs (SAF)

Variable	Placebo *N* = 207	Tamsulosin OCAS 0.4 mg *N* = 200	Tamsulosin OCAS 0.8 mg *N* = 197	Tamsulosin OCAS 1.2 mg *N* = 202
Mean (S.D.) SBP: mmHg				
Baseline	136.3 (16.5)	139.7 (16.0)	139.4 (16.4)	139.5 (17.6)
Change at 12 weeks	−1.9 (14.4)	−3.9 (15.1)	−4.1 (11.7)	−5.1 (14.2)
Mean (S.D.) DBP: mmHg				
Baseline	82.7 (10.3)	84.5 (10.4)	83.5 (10.2)	84.6 (10.5)
Change at 12 weeks	−0.8 (9.5)	−2.7 (9.0)	−1.5 (8.2)	−3.0 (8.9)
Mean (S.D.) PR: bpm				
Baseline	73.0 (10.5)	72.9 (9.9)	72.9 (10.2)	73.7 (10.3)
Change at 12 weeks	−0.1 (9.1)	−0.5 (9.5)	−1.0 (9.5)	−0.1 (10.2)

(4.4%) and, in particular, the 1.2 mg dose (8.1%). Most of the dizziness and abnormal ejaculation cases were considered to be treatment-related in the opinion of the investigator. Two patients reporting treatment-related dizziness discontinued from the study (one on tamsulosin OCAS 0.8 mg and one on 1.2 mg) but none of the cases of abnormal ejaculation led to discontinuation from the study.

A total of 13 patients (1.6%) experienced a serious TEAE: 2 patients (0.9%) on placebo, 2 patients (1.0%) on tamsulosin OCAS 0.4 mg, 4 patients (1.9%) on 0.8 mg and 5 patients (2.4%) on 1.2 mg. These were in the opinion of the investigator treatment-related in 0.5%, 0%, 1.0% and 0.5% of patients treated with placebo or tamsulosin OCAS 0.4, 0.8 or 1.2 mg, respectively. None of the patients died. The number of patients who discontinued due to AEs was low. A total of 19 patients (2.3%) discontinued from the study due to TEAEs (including 8 patients discontinuing due to serious AEs). There were no relevant differences between the tamsulosin OCAS treatment groups (2.9%, 2.4% and 3.3% of patients on 0.4, 0.8 and 1.2 mg, respectively) vs. 0.5% of patients on placebo. The AEs leading to treatment discontinuation were treatment-related in 0.5%, 1.0%, 1.0% and 1.4% of patients treated with placebo or tamsulosin OCAS 0.4, 0.8 or 1.2 mg, respectively

3.3.2. Other safety variables

The mean changes from baseline to endpoint in standing systolic (SBP) and diastolic blood pressure (DBP) and pulse rate (PR) are presented in Table 4. None of the observed changes were of clinical concern and the mean blood pressure and pulse rate remained stable throughout double-blind treatment in all treatment groups.

No mean changes of clinical concern with regard to ECG parameters, laboratory evaluations or the physical examination were observed in any of the treatment groups.

4. Discussion

In this double-blind, randomised, phase 2 dose-response study, all three tamsulosin OCAS doses were

effective and superior to placebo in relieving urinary symptoms and improving disease-specific QoL in patients with LUTS/BPH. Although the absolute mean change in total I-PSS from baseline to endpoint was slightly larger for the tamsulosin OCAS 0.8 and 1.2 mg doses (−8.1 and −8.2, respectively) than for the 0.4 mg dose (-7.6), the mean percentage change vs. baseline was comparable: −42.4% for 0.4 mg, −46.6% for 0.8 mg and −45.2% for 1.2 mg. A literature review on the efficacy of the α_1-AR antagonists alfuzosin, doxazosin, tamsulosin MR capsules and terazosin has shown that these α_1-AR antagonists are equally effective with the percentage improvement in total symptom score ranging between 30% and 45% [5,6]. The improvements seen with all three tamsulosin OCAS doses in this study (42–47%) are at the higher end of this range. Also if the data from this new tamsulosin OCAS formulation is compared with studies using the old MR formulation, the effects observed for all three OCAS doses in this phase 2b study are comparable to those for the tamsulosin MR capsules 0.4 mg. In one US phase 3 study, 254 LUTS/BPH patients who were treated for 13 weeks with tamsulosin MR 0.4 mg had the same baseline characteristics as in the current study: the mean total I-PSS was 19.8 points and mean Q_{max} was 9.5 ml/s [12]. Tamsulosin MR reduced total I-PSS by 8.3 points or 42%. In a recent direct comparative study between alfuzosin 10 mg once daily and tamsulosin MR 0.4 mg once daily with approximately 150 patients per treatment group, the mean total I-PSS at baseline was also comparable to the one in the present phase 2b dose response study with tamsulosin OCAS: 18.0 and 17.4 points, respectively [13]. After 12 weeks, the mean reduction in total I-PSS with both treatments was 6.5 points or 36-37%. The results with all three tamsulosin OCAS doses in the present phase 2b study were again at least comparable.

All three tamsulosin OCAS doses also improved the patients' disease-specific QoL to a significantly greater extent than placebo with no relevant difference between the different doses. The mean IPSS-QoL was improved vs. placebo by 0.4 points with the 0.4 mg dose and by 0.5 points with the 0.8 and 1.2 mg doses. The investigators came to similar conclusions. In their opinion, 86%, 88% and 85% of patients were improved following treatment with tamsulosin OCAS 0.4, 0.8 or 1.2 mg.

Based on the data from this study, it seems that the main difference between the three tamsulosin OCAS doses is related to their tolerability profile. The incidence of AEs is higher with tamsulosin OCAS 1.2 mg than with the 0.8 mg dose and in particular the 0.4 mg dose. TEAEs occurred in 36% vs. respectively 30% and 29%; for treatment-related AEs, the incidences were 17% vs. 13% and 9%. Similar observations were found for common individual TEAEs. The incidence of dizziness was 4.3% vs. 5.8% and 0.5% respectively. For abnormal ejaculation, there was a clear dose-response relationship from 2.0% with 0.4 mg to 4.4% with 0.8 mg and 8.1% with 1.2 mg. The tolerability of the tamsulosin OCAS 0.4 mg dose was most favourable. The percentage of patients reporting at least one treatment-emergent or treatment-related AE was comparable to placebo, which was also the case for dizziness (0.5% with tamsulosin OCAS 0.4 mg and 1.4% with placebo). The incidence of abnormal ejaculation with tamsulosin OCAS 0.4 mg (2.0%) was only marginally higher than with placebo (0.9%). This tolerability profile of tamsulosin OCAS 0.4 mg once daily also seems to be at least as favourable as that of other α_1-AR antagonists including tamsulosin MR 0.4 mg when indirectly compared with data from RCTs [6]. In the European placebo-controlled tamsulosin MR 0.4 mg studies, dizziness occurred in 3.1% of placebo-treated and 3.4% of tamsulosin-treated patients [14]. Abnormal ejaculation occurred to a significantly greater extent with tamsulosin MR (4.5%) than with placebo (1.0%; $p = 0.045$).

The potential benefits of tamsulosin OCAS over other α_1-AR antagonists should be further exploited in future direct comparative studies.

5. Conclusions

All three tamsulosin OCAS doses evaluated in this phase 2b dose-response study (0.4 mg, 0.8 mg and 1.2 mg once daily) were superior to placebo and effective in relieving urinary symptoms and related QoL in patients with LUTS/BPH. Indirect comparison suggests that the reduction in urinary symptoms observed with all three doses is comparable to that reported for other α_1-AR antagonists, including the old tamsulosin MR formulation 0.4 mg once daily. As the tolerability of the 1.2 mg dose was slightly worse than that of the 0.4 mg and 0.8 mg dose, it was decided to investigate the tamsulosin OCAS 0.4 and 0.8 mg doses in a subsequent phase 3a placebo-controlled and active comparator (tamsulosin MR 0.4 mg capsules) trial. In this phase 2b study, tamsulosin OCAS 0.4 mg appeared to have the most favourable efficacy/tolerability ratio, in particular with regard to AEs commonly attributed to α_1-AR blockade such as dizziness and abnormal ejaculation. Although the type of AEs associated with

tamsulosin OCAS 0.4 mg once daily appear to be those commonly attributed to α_1-AR antagonists, the incidence of at least some of these AEs may be lower. The potential benefits of tamsulosin OCAS over other α_1-AR antagonists should be further exploited in future direct comparative studies.

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