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 Placebo and Active Comparator Controlled Phase 3a Study

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Abstract

Objectives: This phase 3a study assessed the efficacy and safety of two different doses of a new formulation of tamsulosin (the oral controlled absorption system: OCAS) in comparison with placebo and the old modified release (MR) formulation of tamsulosin.

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, tamsulosin OCAS 0.4 mg, tamsulosin OCAS 0.8 mg or tamsulosin MR 0.4 mg once daily in a 1:1:2:2 ratio. 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 and vital signs.

Results: A total of 2152 patients were randomised to placebo (N = 357), tamsulosin OCAS 0.4 mg (N = 361), tamsulosin MR 0.4 mg (N = 710) or tamsulosin OCAS 0.8 mg (N = 724). For the mean reduction in total I-PSS from baseline to endpoint, there was no statistically significant difference between tamsulosin OCAS 0.8 mg (8.0 points or 42.4%) and tamsulosin MR 0.4 mg (8.0 points or 43.2%; p = 0.9909). Both tamsulosin OCAS 0.4 mg (7.7 points or 41.7%) and tamsulosin MR 0.4 mg were similarly superior to placebo (5.8 points or 32.0%; p < 0.0001 for both comparisons). The same observations were found for the improvement in the patient’s urinary condition, both in the opinion of the patients and investigators. The two most frequently reported AEs were those commonly associated with α\textsubscript{1}-adrenoceptor (AR) antagonists: dizziness and abnormal ejaculation. The incidence of dizziness was comparable for the 0.4 mg dose (1.4%) and placebo (1.4%) and increased slightly with tamsulosin MR 0.4 mg (1.7%) and tamsulosin OCAS 0.8 mg (2.4%) although none of the comparisons was statistically significant. However, the incidence of abnormal ejaculation more clearly increased from tamsulosin OCAS 0.4 mg (1.9%) to tamsulosin MR (3.1%) and tamsulosin OCAS 0.8 mg (5.3%). Furthermore, whereas the incidence of abnormal ejaculation for tamsulosin MR 0.4 mg and tamsulosin OCAS 0.8 mg was statistically significantly higher than with...
placebo (0.3%), the difference between tamsulosin OCAS 0.4 mg and placebo was not statistically significant. Tamsulosin OCAS 0.4 mg had the lowest incidence of those AEs attributable to α1-AR antagonists and was also associated with the smallest reduction in blood pressure.

**Conclusions:** Tamsulosin OCAS 0.8 mg is not superior to tamsulosin MR 0.4 mg and is associated with a higher incidence of AEs. Therefore, 0.4 mg is the recommended dose of tamsulosin OCAS in the treatment of patients with LUTS/BPH. The efficacy of tamsulosin OCAS 0.4 mg is superior to placebo and comparable to tamsulosin MR 0.4 mg with a tendency towards a better efficacy/tolerability ratio than with tamsulosin MR 0.4 mg.

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**Keywords:** Tamsulosin; Oral controlled absorption system; Modified release formulation; Placebo; Randomised controlled trial; Efficacy; Tolerability

1. Introduction

Lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH) is a common condition 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 therapeutic option for many patients of which α1-adrenoceptor (AR) antagonists are the most frequently prescribed [3]. Following the Medical Therapy Of Prostatic Symptoms (MTOPS) trial, a combination of an α1-AR antagonist with a 5α-reductase inhibitor such as finasteride or dutasteride is recommended for consideration 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 α1-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 most frequently used in clinical practice [8]. This is probably due to this agent’s beneficial effects in relieving LUTS with minimal undesired effects on the cardiovascular system. This apparent uroselectivity is suggested to be related to tamsulosin’s greater selectivity for α1-AR subtypes present and/or functional in the LUT (i.e. α1A and α1D-ARs) over those in the blood vessels (i.e. α1B-ARs, in particular in the elderly), its selective distribution to prostatic tissue as compared to 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 (\(^{C_{\text{max}}}=\)) 24 hours and (3) independence of the pharmacokinetics on food intake, thereby providing a better efficacy/safety ratio [9,10]. 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 [11]. It is this feature of the OCAS formulation that results in more constant delivery of tamsulosin over 24 hours [10]. Certainly phase 1 studies in healthy young subjects have demonstrated that tamsulosin OCAS (under fasting conditions) indeed has more pronounced controlled release characteristics compared to the MR formulation (under fed conditions) providing a lower \(^{C_{\text{max}}}=\) 24-hour plasma concentration than the MR formulation [10]. Furthermore, the pharmacokinetics of tamsulosin OCAS 0.4 mg are not influenced by whether or not the drug is administered with food [10]. A recent phase 2b dose response study demonstrated that both tamsulosin OCAS 0.4 and 0.8 mg once daily are well tolerated and effective compared to placebo, with the 0.4 mg dose having the best efficacy/tolerability ratio [12]. The present paper describes the results of a double-blind, randomised, parallel group, phase 3a study in which tamsulosin OCAS 0.4 mg and 0.8 mg once daily were compared with both placebo and the once daily tamsulosin MR 0.4 mg formulation.

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 and active comparator controlled, parallel group, multi-national (18 countries), multi-centre (138 mainly European centres) phase 3a study with tamsulosin OCAS doses 0.4 mg and 0.8 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, tamsulosin OCAS 0.4 mg, tamsulosin OCAS 0.8 mg or tamsulosin MR 0.4 mg once daily in a 1:1:2:2 ratio. As the prescribing information of tamsulosin MR 0.4 mg indicates that it should be administered after breakfast or the first meal of the day, all treatments were administered in the morning after breakfast with a glass of water. During the 12-week treatment period, patients visited the clinic at 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 (Qmax) ≥ 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 α1-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, presence of a 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 6 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. Likewise patients who were taking or had taken other drugs for LUTS/BPH (i.e. 5α-reductase inhibitors within 3 months and α1-AR antagonists and plant extracts within one month prior to enrolment) or who were hypersensitive to α1-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, αβ-AR antagonists, cholinergics or anti-cholinergics) or were taking or had been taken other investigational drugs within the previous 3 months were excluded from the study.

2.3. Assessment of efficacy

Efficacy was assessed at all visits by means of the I-PSS questionnaire [13]. 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, the patient had to indicate how he would rate his condition at the time of completing the questionnaire, i.e. the I-PSS disease-specific quality of life (QoL) single question to be rated on a scale 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 give a global assessment of the 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 the start of the 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 (probably, possibly or not 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 enrolment and the final visit.

2.5. Statistical methods and sample size

The two primary objectives of the study were to explore firstly whether tamsulosin OCAS 0.8 mg was superior to tamsulosin MR 0.4 mg and secondly whether tamsulosin OCAS 0.4 mg and tamsulosin MR 0.4 mg were comparably superior to placebo.

Tamsulosin OCAS 0.8 mg was considered to be superior to tamsulosin MR 0.4 mg if the difference between the mean change from baseline to endpoint in total I-PSS was ≥1 point. Such a difference would reflect a 35–65% increase of the reported significant difference between placebo and tamsulosin MR 0.4 mg [14,15]. Assuming a standard deviation (S.D.) of 6, then a minimum of 567 evaluable patients per treatment arm were required to achieve a power of 80% for a 2-sided α = 0.05.

Tamsulosin OCAS 0.4 mg and tamsulosin MR 0.4 mg were considered to be superior to placebo if the true difference between the changes from baseline to endpoint in total I-PSS was ≥1.6 points. Assuming a S.D. of 6, then a minimum of 222 evaluable patients per treatment arm were required to achieve a power of 80% for a 2-sided α = 0.05.

Assuming a placebo run-in and double-blind treatment period drop-out rate of each 10% and maintaining a 1:1:2:2 randomisation ratio, a total of 2100 patients had to be enrolled and 1890 patients to be randomised (315 patients to placebo, 315 patients to tamsulosin OCAS 0.4 mg, 630 patients to tamsulosin MR 0.4 mg and 630 patients to tamsulosin OCAS 0.8 mg).

Changes in total I-PSS and voiding/storage sub-scores were subjected to analysis of covariance (ANCOVA) with baseline as covariate with “treatment” as fixed effect and “centre” as a random effect (mixed effect models). The 2 comparisons versus placebo were adjusted for multiplicity using the Bonferroni-Holm adjustment for multiplicity. The Medical Dictionary for Regulatory Activities (MedDRA) was used for the coding of AEs. The two primary objectives of the study were to explore firstly whether tamsulosin OCAS 0.8 mg was superior to tamsulosin MR 0.4 mg and secondly whether tamsulosin OCAS 0.4 mg and tamsulosin MR 0.4 mg were comparably superior to placebo.

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Data on tolerability and safety variables were summarised using descriptive statistics only, except for the 2 most common AEs with tamsulosin OCAS in the phase 2b study (abnormal ejaculation and dizziness) [12] for which pair-wise comparison (per 2 treatments) was performed using a Chi Square test with Bonferroni-Holm adjustment for multiplicity. The Medical Dictionary for Regulatory Activities (MedDRA) was used for the coding of AEs. However, as in all studies with the MR formulation and in the phase 2b tamsulosin OCAS study the Coding System for a Thesaurus of Adverse Reaction Terms (COSTART) was used (which is a less specific coding system than MedDRA), all MedDRA terms related to dizziness (i.e. dizziness, dizziness aggravated and dizziness spell) and abnormal ejaculation (i.e. ejaculation delayed, ejaculation disorder, ejaculation failure, retrograde ejaculation and semen volume decreased) combined were used for this statistical analysis.
3. Results

3.1. Demographics and other baseline characteristics

A total of 2152 patients were randomised to placebo \((N = 357)\), tamsulosin OCAS 0.4 mg \((N = 361)\), tamsulosin MR 0.4 mg \((N = 710)\) or tamsulosin OCAS 0.8 mg \((N = 724)\) once daily (Fig. 1). 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 18.5 points, the mean \(Q_{\text{max}}\) almost 10 ml/s and the mean prostate volume 43–45 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 (107 patients or 5.0%), with no major differences between the 4 treatment groups (Fig. 1). Discontinuation due to TEAEs was the most frequent reason for withdrawal (57 patients or 2.6%). In addition, 18 patients (0.8%) discontinued due to insufficient response and 32 patients (1.5%) for other reasons (including lost to follow-up \((N = 9)\), protocol violations \((N = 3)\), AEs starting during the placebo run-in period \((N = 3)\), death \((N = 3)\), abnormal laboratory values \((N = 1)\) and other non-specified reasons \((N = 13)\)).

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.

3.3. I-PSS questionnaire

The mean change in total I-PSS from baseline to endpoint is shown in Fig. 2. The mean reduction at endpoint with tamsulosin OCAS 0.8 mg (8.0 points or 42.4%) was not statistically significantly different from that with tamsulosin MR 0.4 mg (8.0 points or 43.2%; difference 0.0: \(p = 0.9909\)). The reduction with both tamsulosin OCAS 0.4 mg (7.7 points or 41.7%) and tamsulosin MR 0.4 mg (8.0 points or 43.2%) was statistically significantly larger than with placebo.

![Fig. 1. Flow diagram of the number of patients enrolled, randomised and completing the study per treatment group.](image-url)
The absolute mean change and in particular the percentage mean change in total I-PSS for tamsulosin OCAS (0.4 and 0.8 mg) and tamsulosin MR 0.4 mg was comparable. The changes observed for the voiding and storage I-PSS sub-scores (Table 2) were very similar to those for the total I-PSS.

The effect of the different treatments on the total I-PSS over time is visualised in Fig. 3. It appears that both tamsulosin OCAS 0.4 and 0.8 mg and tamsulosin MR 0.4 mg had a fast and comparable onset of action.

Table 2

Effect of treatment on the voiding and storage I-PSS sub-scores and symptom score responders (ITT)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo N = 350</th>
<th>Tamsulosin OCAS 0.4 mg N = 354</th>
<th>Tamsulosin MR 0.4 mg N = 700</th>
<th>Tamsulosin OCAS 0.8 mg N = 707</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voiding I-PSS: mean (S.D.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>10.6 (3.4)</td>
<td>10.7 (3.4)</td>
<td>10.8 (3.4)</td>
<td>10.9 (3.3)</td>
</tr>
<tr>
<td>Change at endpoint</td>
<td>−3.7 (3.8)</td>
<td>−4.7 (4.0)</td>
<td>−5.0 (4.0)</td>
<td>−5.0 (4.1)</td>
</tr>
<tr>
<td>Difference vs. placebo</td>
<td>−1.0***</td>
<td>−1.2***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference vs. tamsulosin MR 0.4 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Storage I-PSS: mean (S.D.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7.6 (2.6)</td>
<td>7.8 (2.6)</td>
<td>7.8 (2.6)</td>
<td>7.7 (2.6)</td>
</tr>
<tr>
<td>Change at endpoint</td>
<td>−2.2 (2.7)</td>
<td>−3.0 (2.8)</td>
<td>−3.0 (2.7)</td>
<td>−3.0 (2.8)</td>
</tr>
<tr>
<td>Difference vs. placebo</td>
<td>−0.7***</td>
<td>−0.7***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difference vs. tamsulosin MR 0.4 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responders: % of patients</td>
<td>60.9%</td>
<td>71.2%**</td>
<td>75.4%***</td>
<td>73.8%NS</td>
</tr>
</tbody>
</table>

*aReduction in total I-PSS from baseline to endpoint ≥ 25%.
**p < 0.01 vs. placebo.
***p < 0.001 vs. placebo.
NS: not significant vs. tamsulosin MR 0.4 mg.
At the first assessment after 4 weeks of treatment, approximately 75% of the total improvement was achieved. Further improvement was seen with continuation of treatment.

Patients who had at least a 25% improvement in total I-PSS versus baseline were considered to be responders. At endpoint, 60.9% of patients on placebo compared to 71.2%, 75.4% and 73.8% of patients on tamsulosin OCAS 0.4 mg, tamsulosin MR 0.4 mg and tamsulosin OCAS 0.8 mg, respectively, responded (Table 2). The difference between tamsulosin OCAS 0.8 mg and tamsulosin MR 0.4 mg was not statistically significant whereas the difference versus placebo was significant for both tamsulosin OCAS 0.4 mg and tamsulosin MR 0.4 mg.

### 3.4. Improvement of the patient’s condition

The reduction in urinary symptoms was associated with an improvement in the patients’ QoL with significantly greater mean improvements in IPSS-QoL with both tamsulosin OCAS 0.4 mg and tamsulosin MR 0.4 mg than with placebo (Table 3). The difference between tamsulosin OCAS 0.8 mg and tamsulosin MR 0.4 mg was not significant. The mean reduction from baseline to endpoint in IPSS-QoL was similar for tamsulosin OCAS (0.4 and 0.8 mg) and tamsulosin MR 0.4 mg: 1.4 points in all 3 groups.

Also statistically significantly more patients in the tamsulosin OCAS 0.4 mg and tamsulosin MR 0.4 mg groups than in the placebo group were assessed by the investigator as improved: 80% and 82% versus 71% (Table 3). This applied in particular for the percentage of patients who were considered to be much improved. The difference between the percentage of patients who improved on tamsulosin OCAS 0.8 mg (82%) and tamsulosin MR 0.4 mg (82%) was not statistically significant.

### 3.5. 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.

### 3.6. Adverse events

All treatments were well tolerated. The percentage of patients with at least one TEAE was 20% in the placebo and 24–27% in the tamsulosin OCAS (0.4 and 0.8 mg) and tamsulosin MR 0.4 mg groups (Table 4). The same applied for the percentage of patients with at least one possibly or probably treatment-related AE in the opinion of the investigator: 7% for placebo and 11–14% for tamsulosin OCAS or tamsulosin MR. The two most common TEAEs were dizziness and retrograde ejaculation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Tamsulosin OCAS 0.4 mg</th>
<th>Tamsulosin MR 0.4 mg</th>
<th>Tamsulosin OCAS 0.8 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>350</td>
<td>354</td>
<td>699</td>
<td>706</td>
</tr>
<tr>
<td>Baseline: mean (S.D.)</td>
<td>3.8 (1.0)</td>
<td>3.8 (1.1)</td>
<td>3.8 (1.1)</td>
<td>3.8 (1.1)</td>
</tr>
<tr>
<td>Change at endpoint: mean (S.D.)</td>
<td>−1.1 (1.3)</td>
<td>−1.4 (1.3)</td>
<td>−1.4 (1.3)</td>
<td>−1.4 (1.4)</td>
</tr>
<tr>
<td>Difference vs. placebo: adjusted odds ratio</td>
<td>1.53**</td>
<td>1.60***</td>
<td>0.90NS</td>
<td></td>
</tr>
<tr>
<td>Difference vs. tamsulosin MR 0.4 mg: adjusted odds ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% of patients improveda</td>
<td>71.4%</td>
<td>79.6%**</td>
<td>82.3%***</td>
<td>81.5%NS</td>
</tr>
<tr>
<td>Slightly improved</td>
<td>35.7%</td>
<td>33.1%</td>
<td>33.5%</td>
<td>33.0%</td>
</tr>
<tr>
<td>Much improved</td>
<td>35.7%</td>
<td>46.5%</td>
<td>48.7%</td>
<td>48.4%</td>
</tr>
</tbody>
</table>

a According to the investigator at endpoint.
** p < 0.01 vs. placebo.
*** p < 0.001 vs. placebo.
NS: not significant vs. tamsulosin MR 0.4 mg.
Statistical analysis of all dizziness related terms combined showed that none of the 6 comparisons (tamsulosin OCAS 0.4 mg vs. placebo, tamsulosin MR 0.4 mg vs. placebo, tamsulosin OCAS 0.8 mg vs. tamsulosin MR 0.4 mg, tamsulosin MR 0.4 mg vs. tamsulosin OCAS 0.8 mg) was statistically significant (Fig. 4). The incidence of abnormal ejaculation was higher in all active treatment groups than in the placebo group (0.3%), with a tendency to an increase from tamsulosin OCAS 0.4 mg (1.9%) to tamsulosin MR 0.4 mg (3.1%) and further to tamsulosin OCAS 0.8 mg (5.2%). Moreover, whereas the higher incidence with tamsulosin MR 0.4 mg and tamsulosin OCAS 0.4 mg vs. tamsulosin OCAS 0.8 mg was statistically significant (Fig. 4). The incidence of abnormal ejaculation was higher in all active treatment groups than in the placebo group (0.3%), with a tendency to an increase in the incidence from tamsulosin OCAS 0.4 mg (1.9%) to tamsulosin MR 0.4 mg (3.1%) and further to tamsulosin OCAS 0.8 mg (5.2%). Moreover, whereas the higher incidence with tamsulosin MR 0.4 mg and tamsulosin OCAS 0.8 mg was statistically significant versus placebo, there was no statistically significant difference between tamsulosin OCAS 0.4 mg and placebo. The higher incidence with tamsulosin OCAS 0.8 mg as compared to tamsulosin OCAS 0.4 mg was also statistically significant.

A similar trend towards a higher incidence of TEAEs from tamsulosin OCAS 0.4 mg compared with tamsulosin MR 0.4 mg and, in particular, tamsulosin OCAS 0.8 mg was also noticed when TEAEs commonly attributed to blockade of $\alpha_1$-ARs were pooled. This applied to the pooling of non-cardiovascular (i.e. all abnormal ejaculation related TEAEs, headache, asthenia, fatigue, somnolence, rhinitis, nasal dryness, nasal congestion and nasal obstruction), cardiovascular (i.e. all dizziness related TEAEs, palpitations, tachycardia, hypotension, orthostatic hypotension, dizziness postural, syncope, orthostatic/circulatory collapse and depressed level of or loss of consciousness) and all $\alpha_1$-AR blockade related TEAEs together (Table 4). Whereas none of the patients in the placebo or tamsulosin OCAS 0.4 mg group reported orthostatic hypotension, dizziness postural, syncope or orthostatic/circulatory collapse, there were 6 of these events in the tamsulosin MR 0.4 mg and 5 of these events in the tamsulosin OCAS 0.8 mg groups. A depressed level of or loss of consciousness was reported by 2 patients: one on tamsulosin OCAS 0.4 mg and one on tamsulosin MR 0.4 mg.

During double-blind treatment, 3 patients died: 1 on placebo, 1 on tamsulosin MR 0.4 mg and 1 on tamsu-

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Table 4
Treatment-emergent AEs (i.e. MedDRA coded terms) reported by $\geq$2.0% of patients and those commonly attributed to $\alpha_1$-AR blockade (SAF)

<table>
<thead>
<tr>
<th>N (%) of patients with:</th>
<th>Placebo</th>
<th>Tamsulosin OCAS 0.4 mg</th>
<th>Tamsulosin MR 0.4 mg</th>
<th>Tamsulosin OCAS 0.8 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N = 356$</td>
<td></td>
<td>$N = 360$</td>
<td>$N = 709$</td>
<td>$N = 722$</td>
</tr>
<tr>
<td>At least one TEAE</td>
<td>71 (20%)</td>
<td>93 (26%)</td>
<td>168 (24%)</td>
<td>192 (27%)</td>
</tr>
<tr>
<td>At least one treatment-related AE</td>
<td>25 (7%)</td>
<td>40 (11%)</td>
<td>82 (12%)</td>
<td>103 (14%)</td>
</tr>
<tr>
<td>Most common TEAEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (1.4%)</td>
<td>5 (1.4%)</td>
<td>9 (1.3%)</td>
<td>17 (2.4%)</td>
</tr>
<tr>
<td>Retrograde ejaculation</td>
<td>1 (0.3%)</td>
<td>6 (1.7%)</td>
<td>10 (1.4%)</td>
<td>18 (2.5%)</td>
</tr>
<tr>
<td>TEAEs attributed to $\alpha_1$-AR blockade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cardiovascular</td>
<td>7 (2.0%)</td>
<td>16 (4.4%)</td>
<td>36 (5.1%)</td>
<td>57 (7.9%)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>8 (2.2%)</td>
<td>9 (2.5%)</td>
<td>23 (3.2%)</td>
<td>28 (3.9%)</td>
</tr>
<tr>
<td>All$^a$</td>
<td>13 (3.7%)</td>
<td>25 (6.9%)</td>
<td>55 (7.8%)</td>
<td>80 (11.1%)</td>
</tr>
</tbody>
</table>

$^a$Some AEs may occur simultaneously in one patient.

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Fig. 4. Percentage of patients with all dizziness and abnormal ejaculation MedDRA coded terms combined (SAF). Abnormal ejaculation: $p = 0.0140$ for tamsulosin MR 0.4 mg vs. placebo, $p = 0.0002$ for tamsulosin OCAS 0.8 mg vs. placebo and $p = 0.0399$ for tamsulosin OCAS 0.8 mg vs. tamsulosin OCAS 0.4 mg.
losin OCAS 0.8 mg. None of these deaths were considered by the investigators as treatment-related. In addition, 31 patients (1.4%) experienced other serious TEAE during double-blind treatment: 3 patients (0.8%) on placebo, 7 patients (1.9%) on tamsulosin OCAS 0.4 mg, 9 patients (1.3%) on tamsulosin MR 0.4 mg and 12 patients (1.7%) on tamsulosin OCAS 0.8 mg. These were in the opinion of the investigator considered to be treatment-related in none of the patients receiving placebo, 0.3% of patients receiving tamsulosin OCAS 0.4 mg (1 patient with swelling/dyspnoea exacerbated), 0.4% of patients receiving tamsulosin MR 0.4 mg (1 patient with loss of consciousness, 1 patient with paroxysmal arrhythmia and 1 patient with vertigo and orthostatic hypotension) and 0.6% of patients receiving tamsulosin OCAS 0.8 mg (1 patient with atrial fibrillation, 1 patient with cardiac failure and atrial fibrillation, 1 patient with angina pectoris and 1 patient with myocardial infarction).

The number of patients during double-blind treatment who discontinued due to TEAEs was low. A total of 59 patients (2.7%) discontinued from the study due to TEAEs: 6 patients (1.7%) on placebo, 14 patients (3.9%) on tamsulosin OCAS 0.4 mg, 11 patients (1.6%) on tamsulosin MR 0.4 mg and 28 patients (3.9%) on tamsulosin OCAS 0.8 mg. The AEs leading to treatment discontinuation were treatment-related in 0.6%, 1.9%, 1.3% and 2.4% of patients, respectively. None of these treatment-related AEs resulting in discontinuation were reported as SAE with placebo whereas this applied for 1 patient (0.3%; swelling/dyspnoea exacerbated) in the tamsulosin OCAS 0.4 mg, 1 patient (0.1%; vertigo/orthostatic hypotension) in the tamsulosin MR 0.4 mg and 3 patients (0.4%; atrial fibrillation, cardiac failure/atrial fibrillation and angina pectoris) in the tamsulosin OCAS 0.8 mg groups. Of the treatment-related AEs resulting in discontinuation none were of severe intensity in the placebo or tamsulosin OCAS 0.4 mg groups whereas 1 event in 1 patient was severe on tamsulosin MR 0.4 mg (peripheral oedema) and 5 events in 4 patients on tamsulosin OCAS 0.8 mg were severe (headache, atrial fibrillation (twice), diarrhoea and cardiac failure).

**Table 5**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>Tamsulosin OCAS 0.4 mg</th>
<th>Tamsulosin MR 0.4 mg</th>
<th>Tamsulosin OCAS 0.8 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 340</td>
<td>N = 344</td>
<td>N = 691</td>
<td>N = 690</td>
</tr>
<tr>
<td>Mean (S.D.) SBP: mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>139.1 (17.3)</td>
<td>139.3 (17.2)</td>
<td>138.5 (17.1)</td>
<td>138.9 (18.1)</td>
</tr>
<tr>
<td>Change at 12 weeks</td>
<td>−1.5 (14.0)</td>
<td>−2.2 (15.2)</td>
<td>−3.5 (15.5)</td>
<td>−3.5 (15.9)</td>
</tr>
<tr>
<td>Mean (S.D.) DBP: mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>83.7 (10.7)</td>
<td>82.9 (10.2)</td>
<td>83.5 (10.5)</td>
<td>83.3 (10.9)</td>
</tr>
<tr>
<td>Change at 12 weeks</td>
<td>−1.2 (9.5)</td>
<td>−0.5 (9.2)</td>
<td>−2.2 (9.8)</td>
<td>−2.1 (9.4)</td>
</tr>
<tr>
<td>Mean (S.D.) PR: bpm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>73.2 (10.0)</td>
<td>73.1 (9.6)</td>
<td>72.9 (10.4)</td>
<td>73.0 (10.0)</td>
</tr>
<tr>
<td>Change at 12 weeks</td>
<td>−0.3 (9.6)</td>
<td>−0.8 (8.9)</td>
<td>−0.1 (10.4)</td>
<td>+0.2 (10.0)</td>
</tr>
</tbody>
</table>

Number of patients with data after 12 weeks of treatment.

* N = 690 for PR.

* N = 687 for PR.
3.7. Other safety variables

The mean changes in supine systolic (SBP) and diastolic blood pressure (DBP) from baseline to week 12 of treatment are presented in Fig. 5. Table 5 shows the changes in vital signs measured in the standing position. It appears that there were decreases in SBP and DBP in all treatment groups, including the placebo group. Minor reductions were noticed with tamsulosin MR 0.4 mg and tamsulosin OCAS 0.8 mg. However, these reductions were even smaller with placebo and, in particular, tamsulosin OCAS 0.4 mg. The greater reductions in supine SBP and DBP with tamsulosin OCAS 0.8 mg were significant ($p < 0.05$; Fig. 5).

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. Results for placebo, tamsulosin OCAS 0.4 or 0.8 mg and tamsulosin MR 0.4 mg were comparable.

4. Discussion

In this double-blind, randomised, parallel group, phase 3a study involving more than 2000 patients with LUTS/BPH, the new OCAS formulation of tamsulosin at a dose of 0.4 mg and the old MR formulation of tamsulosin at a dose of 0.4 mg were similarly effective and superior to placebo in relieving (bothersome) urinary (storage) symptoms and improving disease-specific QoL. The efficacy of tamsulosin OCAS 0.8 mg was, however, not significantly superior to that of tamsulosin MR 0.4 mg.

Although the absolute mean reduction from baseline to endpoint and the difference versus placebo in total I-PSS in the tamsulosin MR 0.4 mg and tamsulosin OCAS 0.8 groups appeared to be slightly larger than in the tamsulosin OCAS 0.4 mg group, the relative difference of 0.3 points constituted less than 4% of the total reduction in I-PSS from baseline and is too small to be considered as clinically relevant. However, the percentage changes versus baseline were very comparable: a reduction of 42% with tamsulosin OCAS 0.4 mg vs. 42–43% with tamsulosin MR 0.4 mg and tamsulosin OCAS 0.8 mg.

A literature review on the efficacy of the $\alpha_1$-AR antagonists alfuzosin (including the new prolonged release once daily formulation), doxazosin (including the new gastro-intestinal therapeutic system (GITS) formulation), tamsulosin MR and terazosin has shown that these $\alpha_1$-AR antagonists are equally effective with a percentage improvement in total symptom score ranging between 30% and 45% [5,6]. The percentage improvements in total symptom score seen with tamsulosin OCAS and tamsulosin MR in this study (42–43%) are at the higher end of this range.

The observed effects in this phase 3a study with the old MR formulation of tamsulosin are comparable to those reported in previous studies with this formulation [14–17]. In one US phase III study which used the I-PSS questionnaire to assess the effect of treatment on urinary symptoms, 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: mean total I-PSS was 19.8 points and mean $Q_{\text{max}}$ was 9.5 ml/s [14]. Tamsulosin MR 0.4 mg reduced total I-PSS with 8.3 points or 42% which was 2.8 points or 14% larger than that obtained with placebo [14]. The data observed in this phase 3a study with tamsulosin MR 0.4 mg were very comparable with a reduction in total I-PSS from baseline to endpoint of 8.0 points or 43% and an additional improvement over placebo of 2.2 points or 11%. 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 3a study: 18.0 and 17.4 points, respectively [18]. After 12 weeks, the mean reduction in total I-PSS with both treatments was 6.5 points or 36–37%. The results with tamsulosin MR reported in the present phase 3a study are again at least comparable.

The results with tamsulosin OCAS 0.4 and 0.8 mg in this phase 3a study are consistent with those observed in the phase 2b dose response study [12]. In the phase 2b study with a baseline total I-PSS of around 18 points, the improvement in total I-PSS from baseline to endpoint was 7.6–8.1 points or 42–47% compared with 7.7–8.0 points or 42% in the present phase 3a study. The additional improvement over placebo was also similar: 1.6–2.0 points in the phase 2b vs. 1.7–2.0 in the present phase 3a study.

Both tamsulosin OCAS 0.4 mg and tamsulosin MR 0.4 mg also improved the patients’ disease-specific QoL to a comparable and significantly greater extent than placebo with no apparent difference between them. Tamsulosin OCAS 0.8 mg was also not superior to tamsulosin MR 0.4 mg in this regard. The mean improvement in IPSS-QoL from baseline to endpoint was 1.4 points in the 2 tamsulosin OCAS and in the tamsulosin MR treatment groups. The investigators came to similar conclusions. In their opinion, around 80% of patients were improved and around 47% much improved following treatment with tamsulosin OCAS.
0.4 or 0.8 mg or tamsulosin MR 0.4 mg once daily. The effects found with the 2 tamsulosin OCAS doses are again consistent with those reported for the phase 2b study [12].

Although the efficacy of tamsulosin OCAS 0.4 and 0.8 mg and tamsulosin MR 0.4 mg is comparable and in line with those previously reported both for tamsulosin MR 0.4 mg and other α1-AR antagonists, the results of this phase 3a study suggest that there appear to be differences in their safety profile. In line with the results of the phase 2b dose response study [12], the tolerability of the tamsulosin OCAS 0.4 mg dose was more favourable than that seen with tamsulosin OCAS 0.8 mg. There was a higher incidence of dizziness, abnormal ejaculation and cardiovascular, non-cardiovascular or all TEAEs often attributed to α1-AR blockade with incidences of 1.4%, 1.9%, 2.5%, 4.4% and 6.9% with tamsulosin OCAS 0.4 mg and 2.4%, 5.3%, 3.9%, 7.9% and 11.1% with tamsulosin OCAS 0.8 mg. The incidences of these events with tamsulosin OCAS 0.4 mg were furthermore comparable or not very much higher than those on placebo: 1.4%, 0.3%, 2.2%, 2.0% and 3.7%. A comparable incidence of dizziness (0.5% of patients receiving tamsulosin OCAS 0.4 mg and 1.4% of patients on placebo) and a low but slightly higher incidence of abnormal ejaculation (2.0% of patients on tamsulosin OCAS 0.4 mg vs. 0.9% of patients on placebo) was also demonstrated in the phase 2b dose response study [12]. Finally, whereas the higher incidence of abnormal ejaculation with tamsulosin OCAS 0.8 mg (5.3%) was statistically significant versus both placebo (0.3%) and tamsulosin OCAS 0.4 mg (1.9%), the slightly higher incidence of abnormal ejaculation on tamsulosin OCAS 0.4 mg versus placebo was not statistically significant. This lower incidence of TEAEs with tamsulosin OCAS 0.4 mg versus tamsulosin OCAS 0.8 mg was supported by a slightly but statistically significantly smaller reduction in supine BP. It should, however, be noted that the blood pressure reductions with both tamsulosin OCAS doses were small and even smaller with the 0.4 mg dose than with placebo. Overall, based on both the phase 2b dose response and the present phase 3a study, it can definitely be concluded that tamsulosin OCAS 0.4 mg has a more favourable efficacy/safety ratio than tamsulosin OCAS 0.8 mg. Therefore, the 0.4 mg dose is the recommended dose of tamsulosin OCAS for the treatment of patients with LUTS/BPH.

The final question is whether tamsulosin OCAS 0.4 mg is better tolerated or more safe than the old tamsulosin MR formulation at a dose of 0.4 mg, the most commonly used α1-AR antagonist for LUTS/BPH in current clinical practice [5–7]. In the present phase 3a study, the incidence of TEAEs with tamsulosin MR 0.4 mg was intermediate between that of tamsulosin OCAS 0.4 and 0.8 mg with a tendency for a slightly higher incidence with tamsulosin MR 0.4 mg than with tamsulosin OCAS 0.4 mg. The incidence of dizziness, abnormal ejaculation and cardiovascular, non-cardiovascular or all TEAEs often attributed to α1-AR blockade were 1.4%, 1.9%, 2.5%, 4.4% and 6.9% with tamsulosin OCAS 0.4 mg and 1.7%, 3.1%, 3.2%, 5.1% and 7.8% with tamsulosin MR 0.4 mg. This slightly lower incidence of TEAEs with tamsulosin OCAS 0.4 mg versus tamsulosin MR 0.4 mg was supported by a slightly but statistically significantly smaller reduction in supine BP.

It should be noted that the incidence of TEAEs with tamsulosin MR 0.4 mg in this mainly European phase 3a tamsulosin OCAS comparative study was slightly lower than that in previous European placebo-controlled studies with tamsulosin MR 0.4 mg [16,17]. Dizziness occurred in 3.4% of tamsulosin MR-treated patients [17] versus 1.7% in the present study. Abnormal ejaculation occurred to a significantly greater extent with tamsulosin MR (4.5%) than with placebo (1.0%; p = 0.045) [17] but again the incidence in the present study was lower (3.1%). It therefore seems that the AEs data from the present study are the most favourable data reported for tamsulosin MR 0.4 mg so far. In spite of this, tamsulosin OCAS 0.4 mg was even slightly better tolerated and the slightly higher incidence of abnormal ejaculation compared with placebo was not statistically significant, in contrast to tamsulosin MR 0.4 mg. Although abnormal ejaculation is a well tolerated AE and few patients discontinue treatment because of it [19,20], this may be a relevant difference for younger patients.

The data should also be seen in the light of the design of the study as it was set up for registration purposes to demonstrate superior efficacy of tamsulosin OCAS 0.8 mg over tamsulosin MR 0.4 mg and similar superior efficacy of tamsulosin OCAS 0.4 mg and tamsulosin MR 0.4 mg over placebo. The study was not powered for demonstrating a difference in efficacy between tamsulosin OCAS 0.4 mg and tamsulosin MR 0.4 mg, nor for demonstrating a difference in the incidence of AEs between active treatments. Furthermore, tamsulosin MR 0.4 mg was administered according to the prescribing information (after breakfast) whereas when tamsulosin MR 0.4 mg is taken on an empty stomach there is an increased risk of orthostatic hypotension probably due to a higher Cmax [9]. It is not unrealistic that in clinical practice patients do not take their medication strictly according to the patient information sheet and use tamsulosin MR 0.4 mg on an
empty stomach. In contrast, tamsulosin OCAS 0.4 mg pharmacokinetics are not influenced by food [10] and patients are therefore not exposed to an increased risk of orthostatic hypotension when tamsulosin OCAS 0.4 mg is taken on an empty stomach. Whilst the patients included in this registration study may not be fully representative of patients managed in real life clinical practice since patients who are particularly prone to vasodilatatory related AEs such as patients with cardiovascular co-morbidity/medication [21,22] were excluded. Nevertheless, such patients may represent at least 30–40% of those seen in everyday clinical practice [23]. It is important to realise that vasodilatory AEs such as orthostatic hypotension and syncope are not only unpleasant for the patient but can also lead to serious morbidity such as falls and fractures potentially resulting in hospitalisation, nursing home placement and/or death which are associated with huge economic costs for society [22]. Indeed, although never demonstrated in randomised controlled trials with α1-AR antagonists for LUTS/BPH, in an analysis of everyday clinical practice data from the UK, the use of α1-AR antagonists was associated with an approximately double risk for hip/femur fractures in hypertensive patients, whereas no such risk increase was seen upon treatment with other anti-hypertensive drugs [24]. Last but not least, nocturia, the most bothersome complaint in men with LUTS/BPH, is another risk factor for falls and fractures probably due to insufficient lighting and incomplete awakening at night [25,26] which will inevitably be compounded by drugs potentially inducing orthostatic hypotension at night. It therefore seems that the slightly lower incidence of AEs with tamsulosin OCAS 0.4 mg versus tamsulosin MR 0.4 mg in this registration trial may translate into a larger safety advantage and be clinically relevant when these drugs are applied to real life clinical practice. The potential difference in safety between tamsulosin OCAS 0.4 mg and tamsulosin MR 0.4 mg or other α1-AR antagonists when used in clinical practice should be further explored in direct comparative studies, specifically designed to address these issues.

5. Conclusions

In this phase 3a registration study involving more than 2000 LUTS/BPH patients, tamsulosin OCAS 0.8 mg was not superior to tamsulosin MR 0.4 mg in improving urinary symptoms and related QoL. However, tamsulosin OCAS 0.4 mg and tamsulosin MR 0.4 mg were similarly superior to placebo in this regard and can therefore be considered effective treatments for LUTS/BPH. Tamsulosin OCAS 0.4 mg appeared to have the most favourable efficacy/tolerability ratio. Although the categories of AEs associated with tamsulosin OCAS 0.4 mg once daily appear to fall within the groups commonly attributed to α1-AR antagonists, the incidence of these AEs seems to be slightly lower than those seen with tamsulosin MR 0.4 mg and with the higher dose of tamsulosin OCAS 0.8 mg. The 0.4 mg dose is therefore the recommended regimen for tamsulosin OCAS in the treatment of LUTS/BPH. Direct comparative studies specifically designed to explore the potential maximal difference in AEs between tamsulosin OCAS 0.4 mg and other α1-AR antagonists such as tamsulosin MR 0.4 mg and the potential relevance for use in clinical practice should provide more insight into this.

References


