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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 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_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

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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 α_1-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.

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 α_1-adrenoceptor (AR) antagonists are the most frequently prescribed [3]. Following the Medical Therapy Of Prostatic Symptoms (MTOPS) trial, a combination of an α_1-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 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 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 α_1-AR 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 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 [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_{max} with a more constant 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