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The Clinical Development of Omnic (Tamsulosin) Oral Controlled Absorption System (OCAS®)

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1. Introduction

The oral controlled absorption system (OCAS®) is a new improved formulation/delivery system of tamsulosin, called Omnic OCAS. Omnic OCAS gels rapidly and hydrates completely in the upper gastro-intestinal (GI) tract which ensures continuous and consistent drug release throughout the entire length of the GI tract, also in the colon where water is poorly available [1,2]. This leads to improved pharmacokinetics (PK) of Omnic OCAS compared to the existing conventional tamsulosin formulation: 1) lower maximum plasma concentration (C_{max}), 2) more consistent 24-hour plasma concentration or improved C_{max}/C_{24h} ratio and 3) independence of PK of food intake [1,2]. This should improve the efficacy/safety ratio of tamsulosin when treating patients with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH).

2. Design randomised controlled registration trials

For registration purposes in Europe, two randomised controlled clinical trials (RCTs) were performed with Omnic OCAS. The main objectives of these trials were to assess the efficacy and safety and the recommended dose of Omnic OCAS in a relatively healthy and homogeneous population of patients with a relative high severity of LUTS/BPH. The first study was a multi-national, multi-centre, double-blind, randomised, placebo-controlled, parallel group, phase 2b, dose-response study with 3 Omnic OCAS doses: 0.4, 0.8 and 1.2 mg once daily (o.d.) [3]. All 3 OCAS doses were administered in the morning, with or without food (as the PK of Omnic OCAS are not influenced by food intake [1,2]). The second was a multi-national, multi-centre, double-blind, randomised, placebo and active comparator (i.e. the existing conventional tamsulosin 0.4 mg o.d.) controlled phase 3a study with Omnic OCAS 0.4 and 0.8 mg o.d. [4]. All treatments were administered in the morning after breakfast as, according to the labelling, conventional tamsulosin 0.4 mg

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needs to be taken after breakfast or the first meal of the day in order to avoid increased exposure to tamsulosin [5] and limit the risk of orthostatic hypotension [6]. Both studies enrolled patients with a total International Prostate Symptom Score (I-PSS) $\geq$13 and a maximum flow rate (Q_{max}) of 4–12 mL/s, had a single-blind, placebo-run period of 2 weeks and a double-blind, active treatment period of 12 weeks. Patients with significant co-morbidity such as several cardiovascular (CV) diseases (e.g. uncontrolled angina pectoris, myocardial infarction, NYHA class III–IV heart failure, orthostatic hypotension), central nervous system diseases and/or hepatic or renal insufficiency were excluded from the studies. The primary efficacy variable in both studies was the change from baseline to endpoint in total I-PSS.

3. Results randomised controlled registration trials

In total almost 3000 LUTS/BPH patients were randomised in the 2 registration trials of which almost 1700 patients were treated with Omnic OCAS 0.4, 0.8 or 1.2 mg o.d. [3,4]. It appeared that all 3 Omnic OCAS doses were superior to placebo in relieving LUTS and that the efficacy of the 3 doses was comparable (Fig. 1). However, Omnic OCAS 0.4 mg o.d. had a reduced incidence of adverse events (AEs) compared to the 0.8 and 1.2 mg dose (Fig. 2). As the 0.4 mg dose had the most favourable efficacy/tolerability ratio, this dose was chosen as the recommended dose of Omnic OCAS.

Omnic OCAS 0.4 mg was extremely well tolerated compared with placebo: the incidence of dizziness was comparable ($\leq$1.4%) and although the incidence of abnormal ejaculation was slightly higher (around 2% vs. 0.5–1%), the difference was not statistically significant in the phase 3a study (the only study in which statistical analysis for dizziness and abnormal ejaculation as AEs was performed).

In the phase 3a study, the existing conventional tamsulosin 0.4 mg capsule was also investigated [4]. Although this registration trial was not designed nor powered to compare the efficacy and tolerability of both tamsulosin formulations, the clinical efficacy of Omnic OCAS 0.4 mg o.d. and conventional tamsulosin 0.4 mg o.d. was similar (Fig. 3). However, there was a tendency for a slightly lower incidence of AEs with Omnic OCAS 0.4 mg, in particular those commonly associated with α_1-adrenoceptor (AR) antagonists (Fig. 4). This was also reflected by the fact that blood pressure reductions with Omnic OCAS 0.4 mg were at placebo level, whereas these were slightly larger with conventional tamsulosin 0.4 mg than with Omnic OCAS 0.4 mg (Fig. 5). When interpreting these results it should be realised that the circumstances in this RCT were far from ideal to optimally demonstrate the potential difference between OCAS 0.4 mg and conventional tamsulosin 0.4 mg [7]. This

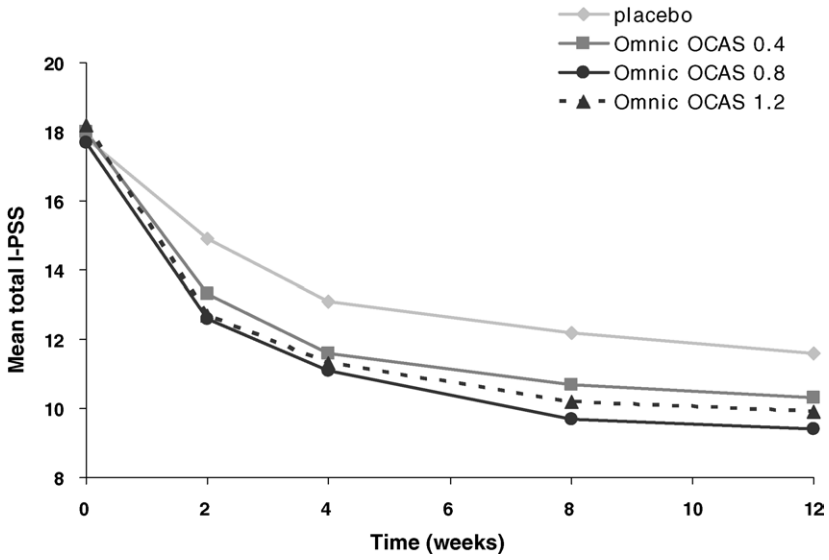

Fig. 1. All 3 Omnic OCAS doses were superior to placebo in improving urinary symptoms with no difference in clinical efficacy between the 3 doses in a phase 2b dose-response study.
$P < 0.001$ for all 3 doses versus placebo. Reprinted from European Urology Supplements, 4(2), Chapple CR, Lorenz JL, Mortensen R, Pauthner H, Reis MO, Schulman CC, van der Putten-Slob I, 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, pp 25–32, 2005, with permission from European Association of Urology [3].