Final study report

Title: A 12 week, multi centre, open label study to evaluate the effect of fesoterodine flexible dosing regimen on the sexual function of women with overactive bladder.

Study acronym: Fesoterodine in OAB

EudraCT: 2010-023851-27
REC number: 12/EE/0029

IRAS: 48710

Co-Sponsors: King's College Hospital

IMP: Fesoterodine Fumarate 4mg and 8 mg

Indication studied: Impact of the sexual function of women with overactive bladder

Study design: This was a multi-centre open label study which aimed to enter 132 female subjects with OAB symptoms. Sexual function and efficacy assessments was evaluated via 3-day bladder diaries, questionnaires (KHQ, PISQ-12, SQoL, PAC-QoL, SAGA, PPBC) and urodynamics. Tolerability and safety was evaluated at every visit with recording of adverse events.

Study initiation date: 14/06/2012

Date of end of trial: 17/02/2017

Chief Investigator: Angie Rantell

Date of Report: 08/03/2018

The trial was conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including, but not limited to, the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments. The study and amendments were reviewed by an independent ethics committee: NRES Committee – London Bridge

SYNOPSIS

Study Title	A 12 week, multi centre, open label study to evaluate the effect of fesoterodine flexible dosing regimen on the sexual function of women with overactive bladder.
Study Centres	The study was carried out at the Urogynaecology department at King's College Hospital, London and St. Mary's Hospital, Paddington, Medway Maritime Hospital, Kent and Croydon University Hospital, London.
First patient's first visit	12/10/2012
Last patient's last visit	17/09/2016
Last dose of IMP taken by a subject	28/06/2016
Date of end of study	17/02/2017
Phase	4
Design summary	This was a multi-centre open label study which aimed to enter 132 female subjects with OAB symptoms. Sexual function and efficacy assessments was evaluated via 3-day bladder diaries, questionnaires (KHQ, PISQ-12, SQoL, PAC-QoL, SAGA, PPBC) and urodynamics. Tolerability and safety was evaluated at every visit with recording of adverse events.
Primary objective	The primary objective is to assess the impact on sexual function, after 12 weeks flexible dose fesoterodine in women with OAB compared to baseline.
Secondary objectives	• To assess the use of flexible dosing of fesoterodine on micturition frequency per 24 hours, nocturnal micturitions per 24 hours, urinary urgency incontinence episodes per 24 hours and urgency episodes per 24 hours after 12 weeks compared to baseline. • To assess the effect of flexible dose fesoterodine on treatment satisfaction and health related quality of life measure at 12 weeks compared to baseline. • To assess the tolerability of flexible dose fesoterodine in women with OAB.

	• To assess the impact of fesoterodine on bowel function. • To assess if changes in sexual function are independent of urodynamic variables
Primary endpoint	Change in item scores of the Pelvic Organ Prolapse and Urinary Incontinence Sexual Questionnaire – short form (PISQ-12) and the Sexual Quality of Life questionnaire (SQOL) at week 12 relative to baseline.
Secondary endpoints	<u>Bladder Diary</u> • Change in mean number of micturitions per 24hours at week 12 relative to baseline. • Change in mean number of nocturnal micturitions per 24 hours at week 12 relative to baseline in subjects with >0 episodes during the 3-day baseline diary period. (Nocturnal micturitions are defined as those occurring between the time the subject goes to bed with the intention of sleeping and the time she rises to start the next day). • Percentage change in urinary urgency incontinence (UUI) episodes per 24 hours at week 12 relative to baseline in subjects with >0 UUI episodes during the 3-day baseline diary period. • Change in mean number of urgency episodes per 24 hours at week 12 relative to baseline. (Urgency episodes are defined as those with a Patient Perception of Intensity of Urgency Score (PPIUS) rating of ≥2 in the diary. • Percentage change in urgency episodes per 24 hours at week 12 relative to baseline. Subtracted Cystometry (in forty subjects only) • Change in first sensation • Change in maximum cystometric capacity • Change in time to first detrusor contraction • Presence of detrusor overactivity **Patient Questionnaires** <u>Patient Perception of Bladder Condition (PPBC)</u> • Change in PPBC at week 12 relative to baseline. <u>King's Health Questionnaire (KHQ)</u> • Change in total score of each domain at week 12 relative to baseline.

	<u>Patient Assessment of Constipation Quality of Life Questionnaire (PAC-QOL)</u> • Change in total score of each domain at week 12 relative to baseline <u>Self Assessment Goal Achievement Questionnaire (SAGA)</u> • Achievement of patient orientated goals at 12 weeks relative to baseline.
Summary of eligibility criteria	1. Female outpatients aged 18 – 80 years. 2. Overactive bladder symptoms (subject reported) for ≥3 months prior to screening visit according to ICS guidelines. 3. Mean number of Urgency episodes ≥3 per 24 hours as verified by the screening bladder diary prior to baseline / Visit 2. 4. Sexually active Able and willing to complete the micturition bladder diaries and all trial related questionnaires, comply with scheduled clinic visits and clinical trial procedures. 5. Capability of understanding and having signed the informed consent form after full discussion of the treatment and its risks and benefits. 6. Able to speak, read and write in English.
Primary efficacy parameter	<u>Prolapse and Incontinence Sexual Quality of Life Questionnaire (PISQ-12)</u> PISQ-12 is a self administered questionnaire consisting of 12 items. <u>Sexual Quality of Life Questionnaire (SQoL)</u> SQoL consists of a set of 18 statements, each asking about thoughts and feelings that subjects may have about their sex life. The statements may be positive or negative. Subjects respond on a 6-point Likert scale ranging from completely agree to completely disagree. It will be administered at visit 2 and 4.
Patient information and consent	yes

IMPs	fesoterodine
Dosing regimen	All patients start on 4mg daily for 28 days then option to either continue on same dose or dose escalate to 8mg for the next 56 days
Sample size	132
No. participants recruited	30
No. withdrawals	2 failed screening 4 withdrew consent 2 lost to follow up 1 withdrawn by investigator 1 withdrawn after SAE
No. participants completing study	20
SAEs reported	0
IMP Dosing and recoded adverse events / important medical events	1 pregnancy reported
Protocol deviations	On occasions visit 1 and 2 performed at same time if patients had received infom prior to appointment and completed three day diary as part of routine care

Conclusions

Primary Outcome

PISQ-12

Paired T-Test PISQ-12 Total Score

Of the 20 subjects tested, the average PISQ-12 score decreased between week 0 ($\overline{x}$ =15.85, SE =1.74) and week 12 ($\overline{x}$ = 11.5, SE = 1.52). This difference of 4.35 points, BCa 95% CIs [7.35, 1.572], was statistically significant $t_{(19)} = 3.159$, $p = 0.005$, and reflects a moderate effect size, $h = 0.542$.

Overall there was mean reduction in PISQ-12 score of 4.35 which was significant (p=0.005). When considering specific questions related to desire, there was very little change in the frequency of sexual desire, the number of orgasms experienced or whether women feel “turned on”. However, by week 12 there was a significant improvement in satisfaction with the variety of sexual activities in the women’s sex life.

SQOL-F

Paired T-Test SQOL-F Total Score

Of the 20 subjects tested, the average SQOL score increased between week 0 ($\bar{x}$ = 66.1, SE = 3.62) and week 12 ($\bar{x}$ = 73.45, SE = 2.42). This difference of -7.35 points, BCa 95% CIs [-2.55, -13], was statistically significant $t_{(19)}$ = -2.673, p = 0.015, and reflects a moderate effect size, h = -0.486.

Secondary Outcomes

Bladder diary variables

Complete bladder diaries were available for 17 subjects. Paired T-Tests were performed to establish differences in bladder diary variables from week 0 to week 12.

Number of episodes of micturition per 24hrs

The average number of episodes of micturition per 24 hrs decreased between week 0 ($\bar{x}$ = 10.05, SE = 0.63) and week 12 ($\bar{x}$ = 6.95, SE = 0.72). This difference of 3.11 episodes, BCa 95% CIs [1.98, 4.26], was statistically significant $t_{(16)}$ = 4.839, p < 0.001, and reflects a large effect size, h = 0.993.

Number of Episodes of nocturia per 24hrs

The average number of episodes of nocturia per 24hrs decreased between week 0 ($\bar{x}$ = 0.82, SE = 0.12) and week 12 ($\bar{x}$ = 0.32, SE = 0.10). This difference of 0.51 points, BCa 95% CIs [0.26, 0.75], was statistically significant $t_{(16)}$ = 4.441, p < 0.001, and reflects a large effect size, h = 0.973.

Number of Episodes of UUI per 24hrs

The average number of episodes of UUI per 24hrs decreased between week 0 ($\bar{x}$ = 1.68, SE = 0.43) and week 12 ($\bar{x}$ = 0.65, SE = 0.45). This difference of 1.02 points, BCa 95% CIs [0.49, 1.59], was statistically significant $t_{(16)}$ = 3.096, p = 0.007, and reflects a moderate effect size, h = 0.502. This represents a 61.3% reduction in UUI episodes per week.

Number of Episodes of U per 24hrs

The average number of episodes of U per day decreased between week 0 ($\bar{x}$ = 4.65, SE = 0.55) and week 12 ($\bar{x}$ = 1.31, SE = 0.38). This difference of 3.34 points, BCa 95% CIs [2.38, 4.39], was statistically significant $t_{(16)}$ = -5.95, p = 0.00, and reflects a large effect size, h = 1.524.

Number of Episodes of U per 3 day diary

The average number of episodes of U per week decreased between week 0 ($\bar{x}$ = 13, SE = 1.4) and week 12 ($\bar{x}$ = 4.12, SE = 1.13). This difference of 8.88 episodes, BCa 95% CIs [6.14, 11.5], was

statistically significant $t_{(16)} = 6.862$, $p < 0.001$, and reflects a large effect size, $h = 1.51$. This represents a 68.3% reduction in urgency episodes per week.

KHQ

Paired T-Test King's Health Questionnaire (KHQ) Total Score

Of the 20 subjects tested, the average KHQ score decreased between week 0 ($\bar{x} = 520.18$, SE = 40.2) and week 12 ($\bar{x} = 288.21$, SE = 43.48). This difference of 231.97 points, BCa 95% CIs [302.41, 164.64], was statistically significant $t_{(19)} = 6.892$, $p < 0.001$, and reflects a large effect size, $h = 1.126$.
There were significant changes in every domain of the KHQ with the greatest changes observed in role limitations, emotions and incontinence impact domains (mean difference of 35.01, 32.8, 30.84 respectively). The least change was seen in the general health perception and present problems domains (mean difference 5.0 and 5.15 respectively).

PAC-QOL

Paired T-Test PACQOL Total Score

Of the 20 subjects, the average PACQOL score decreased between week 0 ($\bar{x} = 28.25$, SE = 5.57) and week 12 ($\bar{x} = 25.6$, SE = 4.5). This difference of 2.65 points, BCa 95% CIs [8.97, -3.65], was not statistically significant $t_{(19)} = 0.716$, $p = 0.483$, it reflects a small effect size, $h = 0.106$.
There were no significant differences noted in any domain of the PAC-QOL questionnaire.

PPBC

Paired T-Test Patient Perception of Bladder Condition (PPBC)

Of the 20 subjects, the average PPBC score decreased between week 0 ($\bar{x} = 4.55$, SE = .24) and week 12 ($\bar{x} = 3.2$, SE = .24). This difference of 1.35 points, BCa 95% CIs [1.8, 0.9], was statistically significant $t_{(19)} = 5.81$, $p < 0.001$, and reflects a large effect size, $h = 1.165$.

SAGA

When considering overall goal achievement in the study only one subject did not achieve her goals with a further 35% somewhat achieving their goals. 60% of subjects achieved their goals with 40% of those exceeding or greatly exceeding their expectations.

Although this study did not proceed as planned, the results of the secondary outcomes are in keeping with most other clinical trials using fesoterodine. Given these similarities, it could be suggested that as there were trends towards improvement in the primary outcome measures, that as a proof of concept study, this does confirm that this is an appropriate area for investigation and that there is potential for a positive benefit of fesoterodine for the treatment of OAB on women's SF. However, further investigation into the sample population is necessary to determine the scope of the problem and understand how to identify these women in practice so that appropriate and reliable sampling methods can be developed for future studies.

Author:

SIGNATURE:

DATE: