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**COMPOUND NUMBER:** UK-369,003

**THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:** Not Applicable

**NCT NO.:** NCT00457457

**PROTOCOL NO.**: A3711044

**PROTOCOL TITLE**: A Multi-Center, Randomized, Parallel Group, Double-Blind, Placebo Controlled Proof of Concept and Dose Ranging Study with an Active Control to Assess the Efficacy and Safety/Tolerability of UK-369,003 Immediate Release (IR) and Modified Release (MR) in the Treatment of Men with Lower Urinary Tract Symptoms (LUTS) with and without Erectile Dysfunction (ED)

**Study Center(s):** 45 centers (Australia: 2 centers; Belgium: 3 centers; Canada: 3 centers; Chile: 2 centers; Columbia: 5 centers; Denmark: 3 centers; Finland: 4 centers; Greece: 3 centers: Italy: 2 centers; Latvia: 1 center; Lithuania: 3 centers; Poland: 5 centers; Slovakia: 5 centers; Spain: 3 centers: United Kingdom: 1 center).

**Study Initiation and Completion Dates:** 18 May 2007 to 16 April 2008

**Phase of Development**: Phase 2

**Study Objective(s):**

- Compare the efficacy of the 100 mg MR and 40 mg IR formulations of UK-369,003 versus placebo in men suffering from LUTS with and without ED.
- Characterize the dose response relationship of the UK-369,003 MR formulation in the treatment of men with LUTS with and without ED.
- Investigate the efficacy of UK-369,003 MR doses relative to UK-369,003 40 mg IR.
- Investigate the efficacy of UK-369,003 MR doses relative to tamsulosin 0.4 mg prolonged release (PR).
- To evaluate the safety and tolerability of UK-369,003 in men with LUTS with and without ED.

## METHODS

**Study Design:** This was a multi-center, double-blind, placebo-controlled parallel group study in adult males with LUTS.

For each subject, the study consisted of an initial screening visit at 4 weeks prior to double-blind treatment (Week -4, Visit 1), a 2-week single-blind placebo run-in period at 2 weeks prior to double-blind treatment (Week -2, Visit 2) , a baseline visit (Week 0, Visit 3), a 12-week double-blind treatment period (with visits at Weeks 1, 2, 4 and 12, Visits 4, 5, 6 and 7), and a follow-up visit at 1 week after last study drug dose (Week 13, Visit 8). If a subject withdrew before completing the study, assessments were carried out at the time of last study drug dose at an early termination post baseline visit (Visit 9).

For subjects on α-blockers, anti-muscarinics and/or phosphodiesterase 5 (PDE5) inhibitor medications a 4-week washout period prior to double-blind treatment started at Week -4 (Visit 1) and ran concomitantly with the single-blind placebo run-in period starting at Week -2, Visit 2).

Randomized subjects were stratified into 2 groups: either with ED or without ED; with no more than 299 subjects in the LUTS with ED stratum and 207 subjects in the LUTS without ED stratum.

**Number of Subjects (Planned and Analyzed):** A total sample size of 414 subjects (54 subjects in the UK-369,003 10 mg MR, 25 mg MR and 50 mg MR groups, 90 subjects in the UK-369,003 100 mg MR and UK-369,003 40 mg IR groups, 36 subjects in the tamsulosin 0.4 mg PR group, and 36 Subjects in the placebo group) was planned. Of the 609 subjects screened, 419 subjects completed screening and 418 subjects were randomized. Of the 418 randomized subjects, 415 were treated and included in the full analysis set (FAS), and 346 subjects were included in the per protocol analysis set (PPAS).

**Diagnosis and Main Criteria for Inclusion:** Subjects were male, aged ≥40 years, with documented LUTS with an International Prostate Symptom Score (IPSS) of ≥13 points at both screening and baseline, a clinical diagnosis of benign prostate hyperplasia (BPH), and a maximum urine flow rate ($Q_{max}$) of 5 to 15 mL/second with a voided volume of ≥150 mL.

Subjects were excluded if they had a history, evidence or suspicion of prostate cancer, a post-void residual urine volume >200 mL, a urinary tract infection, a positive (≥1+) hematuria result for urine dipstick test, a history of urological surgery or procedures, a persistent local lower urinary tract pathology, neurological diseases known to affect bladder function, loss of vision in 1 eye due to non-arteritic ischemic optic neuropathy, or hereditary degenerative retinal disorders.

Subjects receiving α-blockers, muscarinic receptor antagonists, PDE5 inhibitors, agents known to affect vesico-urethral function or erectile function, 5-α-reductase inhibitors, diuretics, beta-blockers or other anti-hypertensive agents, nitrates or nitric oxide donors, cytochrome P450 inhibitors, or warfarin were also excluded.

**Study Treatment:** Subjects were randomized to 1 of the following 7 treatment groups for 12-weeks of double-blind treatment according to the ratio 3:3:3:5:5:2:2:

- UK-369,003 10 mg MR (one 10 mg tablet)
- UK-369,003 25 mg MR (one 25 mg tablet)
- UK-369,003 50 mg MR (one 50 mg tablet)
- UK-369,003 100 mg MR (one 100 mg tablet)
- UK-369,003 40 mg IR (two 20 mg tablets)
- Tamsulosin 0.4 mg PR (one 0.4 mg tablet)
- Placebo

Study treatment was taken once daily between 11:00 and 13:00: 7 tablets were taken with water and swallowed whole without chewing, 1 after the other.

During the 2-week placebo run-in period, each subject received placebo matching the active treatment group tablets (7 tablets: 1 tablet each for the UK-369,003 10 mg MR, 25 mg MR, 50 mg MR and 100 mg MR and tamsulosin 0.4 mg PR doses and 2 tablets for the UK-369,003 40 mg IR dose), once daily for 2 weeks.

During the double-blind treatment period, each subject received either active tablets, or placebo matching active treatment group tablets, once daily for 12 weeks.

**Efficacy Evaluations:**

***International Prostate Symptom Score (IPSS)***

Subjects were asked to complete the 1-week recall period version of the IPSS at screening, run-in, baseline, Weeks 1, 2 and 4, and end of treatment (Week 12)/early withdrawal (Visits 1 to 7/early withdrawal).

***International Index of Erectile Function - Erectile Function (IIEF-EF) Domain***

Subjects were asked to complete Questions 1 to 5 and Question 15 of the IIEF, which comprise the EF domain, at baseline, Week 4 and end of treatment (Week 12)/early withdrawal (Visits 3, 6 and 7/early withdrawal).

***International Consultation on Incontinence Questionnaire - Male Lower Urinary Tract Symptoms (ICIQ-MLUTS)***

Subjects were asked to complete the ICIQ-MLUTS long form at screening, baseline, Week 4, and end of treatment (Week 12)/early withdrawal (Visits 1, 3, 6 and 7/early withdrawal).

***Quality of Erection Questionnaire (QEQ)***

Subjects were asked to complete 2 questions (Question 5 on the hardness of erection and Question 6 on the overall quality of erection) at baseline, Week 4 and end of treatment (Week 12)/early withdrawal (Visits 3, 6 and 7/early withdrawal).

***Patient Reported Treatment Impact (PRTI) Questionnaire***

Subjects were asked to complete the PRTI at end of treatment (Week 12)/early withdrawal (Visit 7/early withdrawal).

***Lower Urinary Tract Symptoms (LUTS) Diary***

Subjects completed a real time urinary diary for 72 hours (3 or 4 consecutive days) within a 5-day period immediately prior to the baseline, Week 2, Week 4, and end of treatment (Week 12)/early withdrawal visits (Visits 3, 5, 6 and 7/early withdrawal).

***Uroflowmetry***

Maximum urinary flow rate ($Q_{max}$) was an objective assessment of the voiding function of the lower urinary tract measured at screening, baseline, Week 1, Week 4 and end of treatment (Week 12)/early termination (Visits 1, 3, 4, 6 and 7/early termination). If a subject failed to produce a voided volume ≥150 mL at the first attempt, a second attempt could be made. A $Q_{max}$ with voided volume <150 mL was considered invalid.

**Pharmacokinetic Evaluations:** Blood samples for population pharmacokinetics were collected at baseline, and Weeks 1, 4 and 7/early withdrawal (Visits 3, 4, 6 and 7/early withdrawal).

**Safety Evaluations:** Adverse events (AEs) were monitored throughout the study. Laboratory tests (hematology, chemistry and urinalysis) on blood and urine samples were performed at the screening and end of treatment (Week 12)/early withdrawal visits (Visits 1 and 7/early withdrawal), and also at follow-up (Visit 8) if required. Subjects were assessed with a supine 12-lead electrocardiogram at screening. Post-void residual (PVR) volume of urine was measured by ultrasound scan at the screening, baseline and end of treatment (Week 12)/early withdrawal visits (Visits 1, 3 and 7/early withdrawal). Vital signs were assessed at screening, baseline, Weeks 1, 2, 4, and end of treatment (Week 12)/early withdrawal (Visit 1 and Visits 3 to 7/early withdrawal).

**Statistical Methods:**

***Primary Efficacy Endpoint***

The primary endpoint was the change in the $IPSS_{total}$ from baseline (Visit 3) to end of treatment (Week 12)/early withdrawal (Visit 7/early withdrawal).

The $IPSS_{total}$ was defined as the sum of the scores of non-missing items of the IPSS Questions 1 to 7. If the number of missing items was more than 3, then the $IPSS_{total}$ was

missing. Each individual question was scored as 0 to 5. The $IPSS_{total}$ was 0 to 35. The change in $IPSS_{total}$ from baseline (Visit 3) to end of treatment (Week 12)/early withdrawal (Visit 7/early withdrawal), where end of treatment was denoted as y, was calculated as:

$$y=IPSS_{total} \text{ (end of treatment/early termination) - } IPSS_{total} \text{ (baseline)}$$

Due to the Bayesian approach used for the sample size estimation, Bayesian statistical methods were used for the analysis in the overall group (including subjects with LUTS with and without ED). The primary analysis was based on the FAS (subjects who received ≥1 dose of double-blind treatment and had ≥1 efficacy assessment on double-blind treatment) with missing data imputed by the last observation carried forward (LOCF) method. Models included terms for randomization stratum and appropriate baseline. The posterior mean and the associated 90% credible intervals were calculated and presented. The posterior probabilities of giving a difference from placebo of ≤-2.5 were calculated for the UK-369,003 100 mg MR and UK-369,003 40 mg IR treatment groups.

The IPSS change from baseline (Visit 3) was analyzed for the PPAS (subjects who completed 12 weeks of double-blind treatment at >80% treatment compliance without violating any inclusion or exclusion criteria or the protocol) in the same way as for the FAS.

To assess the dose response for the UK-369,003 10 mg MR, 25 mg MR, 50 mg MR and 100 mg MR doses, the primary endpoint was modeled using a normal dynamic linear model (NDLM) in the overall group (including subjects with LUTS with and without ED), based on the FAS with LOCF approach for missing values. Estimates of the model parameters were presented and the estimated dose-response curve with 90% credible interval bounds was plotted. Posterior probabilities of being ≥2 points better than placebo were also calculated.

The dose-response was explored for the PPAS in the same way as for the FAS.

In addition, descriptive statistics and plots were produced to summarize:

- The $IPSS_{total}$ by treatment and visit.
- The change in $IPSS_{total}$ from baseline (Visit 3) to Weeks 1, 2, 4 and end of treatment (Week 12)/early withdrawal (Visits 4, 5, 6 and 7/early withdrawal) by treatment.
- Cumulative frequency distribution of the change in the $IPSS_{total}$ from baseline (Visit 3) to end of treatment (Week 12)/early withdrawal (Visit 7/early withdrawal) by treatment.

***Secondary Efficacy Endpoints***

The secondary endpoints were analyzed in a similar way as for the primary endpoint. Descriptive statistics were produced to summarize:

- $Q_{max}$, the 2 IPSS sub-scores and the individual IPSS questions by treatment, and visit.

- The IIEF-EF domain score and the QEQ score by treatment and visit for the overall group (including subjects with LUTS with and without ED), and for the sub-group of subjects with LUTS with ED.

- Responder rate based on a 25% reduction in the $IPSS_{total}$ from baseline (Visit 3) to subsequent visits.

For the IPSS sub-scores, descriptive statistics and plots were produced showing the raw means for the UK-369,003 10 mg MR, 25 mg MR, 50 mg MR and 100 mg MR dose groups and placebo. These plots were produced for the overall group (including subjects with LUTS with and without ED).

A subject was defined as a responder if the ratio of the reduction in the $IPSS_{total}$ at the end of treatment (Week 12)/early withdrawal (Visit 7/ early withdrawal) compared to baseline (Visit 3) was at least 25%, ie:

- Responder=1 if ($IPSS_{total}$ (baseline)-$IPSS_{total}$ (end of treatment))/$IPSS_{total}$ (baseline) ≥25%.

- Responder=0 if ($IPSS_{total}$ (baseline)-$IPSS_{total}$ (end of treatment))/$IPSS_{total}$ (baseline) <25%.

Responder rate was analyzed using a Bayesian model with terms for treatment, stratified factor and other covariates as appropriate. The treatment differences for UK-369,003 100 mg MR versus placebo, UK-369,003 40 mg IR versus placebo and UK-369,003 10 mg MR, 25 mg MR, 50 mg MR and100 mg MR versus tamsulosin 0.4 mg PR, were estimated by odds ratios with 2-sided 90% CIs. The observed and predicted responder rates with 2-sided 90% CIs were presented for each treatment group.

***Other Efficacy Endpoints***

LUTS Diary

The following measures were recorded or derived from the LUTS Diary and analyzed for the FAS in the same way as $Q_{max}$: volume of urine voided, frequency of urgency episodes and the severity of urgency episodes, micturition frequency, nocturnal frequency (from time going to bed to time waking up), micturition episodes associated with urgency, IEF, change in mean volume voided per micturition after 2, 4 and 12 week's double-blind treatment, percentage and absolute change in urgency episode frequency after 2, 4 and 12 weeks of double-blind treatment, mean severity and percentage and absolute change in mean severity of urgency episodes after 2, 4 and 12 weeks of double-blind treatment, percentage and absolute change in micturition frequency after 2, 4 and 12 weeks of double-blind treatment, percentage and absolute change in nocturnal frequency after 2, 4 and 12 weeks of double-blind treatment, percentage and absolute change in NMF after 12 weeks of double-blind treatment, percentage and absolute change in micturition episodes associated with urgency after 2, 4 and 12 weeks of double-blind treatment, percentage and absolute change in IEF after 2, 4 and 12 weeks of double-blind treatment.

ICIQ-MLUTS Long Form Questionnaire

For each individual question, the score, degree of the bother and the change from baseline (Visit 3) in the degree of bother for each specific symptom was listed and summarized by treatment and visit. Plots were produced for the subject profiles of the score of each specific symptom at Week 4 and end of treatment (Week 12)/early withdrawal versus baseline (Visit 3).

Patient Reported Treatment Impact Questionnaire (PRTI)

The 5-level response to each individual question was analyzed using a proportional odds logistic regression model with terms for treatment, the stratified factor. The treatment differences for UK-369,003 100 mg MR versus placebo and UK-369,003 40 mg IR versus placebo were estimated with 2-sided 90% CIs. The estimated proportions of each level of response with 2-sided 90% CIs were presented for each treatment group.

***Pharmacokinetics***

Samples for population pharmacokinetics were assayed using a validated analytical method in accordance with Pfizer Standard Operating Procedures. Methods and results of the population pharmacokinetics analyses will be presented in a separate report.

***Safety***

No formal hypothesis testing of safety data was to be performed. Results from the safety assessments (including PVR) and any AEs were presented in tabular and/or graphical format adhering to current Pfizer Data Standards. Safety data were presented based on the safety analysis set (SS; randomized subjects who received ≥1 dose of study treatment).

**RESULTS**

**Subject Disposition and Demography:**

Of the 609 subjects screened, 419 subjects completed screening and 418 subjects were randomized to 1 of 7 treatment groups (Table S1). A total of 381 subjects completed the study, and 34 subjects discontinued: 2 subjects (3.8%), 3 subjects (5.4%), 5 subjects (9.3%), 10 subjects (11.0%) and 8 subjects (8.9%) in the UK-369,003 10 mg MR, 25 mg MR, 50 mg MR, 100 mg MR, and 40 mg IR groups, and 2 subjects (5.6%) in the tamsulosin 0.4 mg PR group, and 4 subjects (10.5%) in the placebo group. Of the 418 randomized subjects, 415 were treated and included in the FAS, and 346 subjects were included in the PPAS.

Demographic characteristics were similar for all treatment groups (Table S2). Summary statistics for LUTS at baseline are presented in Table S3.

## Table S1. Disposition

| | 10 mg MR | 25 mg MR | UK-369,003 50 mg MR | 100 mg MR | 40 mg IR | Tamsulosin 0.4 mg PR | Placebo |
|---|---|---|---|---|---|---|---|
| Number (%) of subjects | | | | | | | |
| Randomized | 53 | 56 | 54 | 91 | 90 | 36 | 38 |
| Treated | 53 | 56 | 53 | 90 | 89 | 36 | 38[a] |
| Completed | 51 (96.2) | 53 (94.6) | 48 (88.9) | 80 (87.9) | 81 (90.0) | 34 (94.4) | 34 (89.5) |
| Discontinued | 2 (3.8) | 3 (5.4) | 5 (9.3) | 10 (11.0) | 8 (8.9) | 2 (5.6) | 4 (10.5) |
| AE | 1 (1.89) | 1 (1.79) | 3 (5.56) | 6 (6.59) | 4 (4.44) | 1 (2.78) | 0 |
| Protocol deviation | 0 | 1 (1.79) | 0 | 0 | 1 (1.11) | 0 | 1 (2.63)[a] |
| Other | 0 | 1 (1.79) | 1 (1.85) | 0 | 0 | 0 | 1 (2.63)[b] |
| No longer willing to participate | 1 (1.89) | 0 | 1 (1.85) | 4 (4.40) | 3 (3.33) | 1 (2.78) | 2 (5.26) |
| Analyzed for efficacy | | | | | | | |
| FAS | 53 (100.0) | 56 (100.0) | 53 (98.1) | 90 (98.9) | 89 (98.9) | 36 (100.0) | 38 (100.0) |
| PPAS | 43 (81.1) | 48 (85.7) | 44 (81.5) | 74 (81.3) | 72 (80.0) | 32 (88.9) | 33 (86.8) |
| Analyzed for safety | | | | | | | |
| AEs | 53 (100.0) | 56 (100.0) | 53 (98.1) | 90 (98.9) | 89 (98.9) | 36 (100.0) | 38 (100.0) |
| Laboratory data | 53 (100.0) | 56 (100.0) | 49 (90.7) | 85 (93.4) | 87 (96.7) | 36 (100.0) | 35 (92.1) |

MR=modified release; IR=immediate release; PR=prolonged release; AE=adverse event; FAS=full analysis set; PPAS=per protocol analysis set

[a] One subject was withdrawn after randomization but before treatment, but is recorded in the summary tables as having received treatment

[b] One subject was withdrawn during follow-up period

## Table S2. Demography

| | 10 mg MR | 25 mg MR | UK-369,003 50 mg MR | 100 mg MR | 40 mg IR | Tamsulosin 0.4 mg PR | Placebo |
|---|---|---|---|---|---|---|---|
| Number of subjects | 53 | 56 | 53 | 90 | 89 | 36 | 38 |
| Mean age (SD), years | 61.3 (8.0) | 62.1 (7.8) | 60.5 (8.1) | 60.8 (8.3) | 60.9 (7.1) | 61.8 (6.9) | 60.6 (7.6) |
| Race, n (%) | | | | | | | |
| White | 45 (84.9) | 49 (87.5) | 46 (86.8) | 81 (90.0) | 82 (92.1) | 33 (91.7) | 35 (92.1) |
| Other | 8 (15.1) | 7 (12.5) | 7 (13.2) | 9 (10.0) | 7 (7.9) | 3 (8.3) | 3 (7.9) |
| Mean BMI (SD), $kg/m^2$ | 27.2 (3.5) | 27.1 (3.4) | 27.8 (3.2) | 26.9 (3.4) | 27.1 (3.6) | 27.5 (4.4) | 26.6 (3.1) |

MR=modified release; IR=immediate release; PR=prolonged release; SD=standard deviation; BMI=body mass index

**Table S3. Mean (SD) for Efficacy Endpoints at Baseline**

| | UK-369,003 | | | | | | |
|---|---|---|---|---|---|---|---|
| | **10 mg MR** | **25 mg MR** | **50 mg MR** | **100 mg MR** | **40 mg IR** | **Tamsulosin 0.4 mg PR** | **Placebo** |
| Number of subjects | 53 | 56 | 53 | 90 | 89 | 36 | 38 |
| $IPSS_{total}$ | 16.7 (4.53) | 17.9 (5.25) | 17.3 (4.60) | 16.8 (4.05) | 17.2 (3.98) | 18.1 (3.86) | 18.8 (4.32) |
| Mean voided volume | 199.9 (63.74) | 184.2 (49.59) | 198.5 (57.42) | 209.2 (77.19) | 202.6 (58.44) | 185.7 (68.20) | 197.6 (45.75) |
| Micturition frequency | 9.2 (2.95) | 9.5 (2.28) | 9.8 (2.95) | 9.2 (2.81) | 9.3 (2.43) | 9.8 (2.76) | 9.9 (2.47) |
| Urgency episode frequency | 6.5 (4.08) | 7.3 (3.76) | 6.9 (3.48) | 7.9 (3.64) | 7.7 (3.38) | 8.1 (3.83) | 8.4 (3.24) |
| Incontinence episode frequency | 0.2 (0.74) | 0.3 (1.37) | 0.3 (1.58) | 0.2 (0.71) | 0.1 (0.53) | 0.0 (0.10) | 0.2 (0.67) |

MR=modified release; IR=immediate release; PR=prolonged release; SD=standard deviation; BMI=body mass index

**Efficacy Results:**

This study incorporated a Bayesian approach utilizing data from prior studies, albeit the placebo response rate observed in the raw data from this study was higher than that observed in the prior data.

Bayesian 2-sample analysis indicated that the mean reductions from baseline in $IPSS_{total}$ for UK-369,003 100 mg MR and UK-369,003 40mg IR were -2.9 and -2.5 points greater than placebo, respectively. The posterior probabilities of achieving a difference better than placebo of ≥2.5 points were ≥50% for both UK-369,003 100 mg MR and 40 mg IR. The dose response for UK-369,003 MR, characterized using an NDLM, showed increasing efficacy with increasing doses. Mean reductions of >2 points were estimated for UK-369,003 25 mg MR, 50 mg MR and 100 mg MR with posterior probabilities of achieving a difference >2 points better than placebo of 59%, 77% and 82%, respectively. Bayesian 2-sample analyses showed the probability of the mean treatment difference being >0 compared with tamsulosin 0.4 mg PR was >50% for UK-369,003 25 mg MR, 50 mg MR and 100 mg MR doses with increasing probability with increasing dose.

Bayesian 2-sample analysis showed improvement in both the storage and voiding subscores of the IPSS for the UK-369,003 100 mg MR and 40 mg IR compared to placebo. There was an approximate 75% posterior probability of achieving an improvement greater than tamsulosin 0.4 mg PR in the storage subscale for each dose of UK-369,003 MR. There was an increasing posterior probability of approximately 30%-80% of achieving an improvement greater than tamsulosin 0.4 mg PR in the voiding subscale with increasing dose of UK-369,003 MR.

There were a higher percentage of responders in all UK-369,003 treatment groups compared to placebo with no apparent dose response or differentiation between MR and IR formulations. There was a greater chance of being a responder in the UK-369,003 10 mg MR, 50 mg MR, and 100 mg MR treatment groups compared to tamsulosin 0.4 mg PR with odds ratios of 1.7 and 1.4 in the UK-369,003 50 mg MR and 100 mg MR treatment groups, respectively.

Improvements in $Q_{max}$ of 2.1 mL/sec and 0.84 mL/sec were observed for UK-369,003 100 mg MR and 40 mg IR compared to placebo, respectively. Bayesian 2-sample analysis showed high posterior probabilities (72.5% to 97.9%) of being better than tamsulosin 0.4 mg PR in the UK-369,003 10 mg MR, 50 mg MR and 100 mg MR treatment groups.

Change from baseline results for the UK-369,003 MR, IR and tamsulosin PR treatment groups in over active bladder endpoints (voided volume per micturition, micturition frequency per 24 hours, urgency episodes per 24 hours, and incontinence episodes per 24 hours) were small and inconsistent with no apparent dose response or treatment effects compared to placebo observed.

In subjects with ED, all doses of UK-369,003 MR and IR improved the IIEF-EF domain score compared with both placebo and tamsulosin 0.4 mg PR. There was a posterior probability of >99% of UK-369,003 100 mg MR and 40 mg IR achieving an improvement greater than placebo, and a probability of >99% for all doses of UK-369,003 achieving an improvement over tamsulosin 0.4 mg PR. Summary statistics for the QEQ demonstrated an improvement for all UK-369,003 treatment groups compared with placebo and tamsulosin 0.4 mg PR, with a similar trend observed in subjects without ED.

For the IPSS QoL question, the change from baseline at Week 12 was similar for all treatment groups (range -0.9 points to -1.5 points); the maximum decrease from baseline was observed in the UK-369,003 40 mg IR treatment group, and the minimum decrease from baseline was observed in the placebo treatment group. Based on the ICIQ-MLUTS questionnaire, improvements in voiding frequency, storage domain and post micturition scores, and associated bother, were observed for all treatment groups, including placebo. For the PRTI questionnaire, a subject was more likely to report greater satisfaction, preference and willingness to reuse UK-369,003 100 mg MR and 40 mg IR compared to placebo; and greater satisfaction, preference and willingness to reuse any UK-369,003 MR dose compared toUK-369,003 40 mg IR or tamsulosin 0.4 mg PR.

**Pharmacokinetic, Pharmacodynamic, and/or Other Results:**

Future anonymized pharmacogenomic analyses will be presented in a separate report.

Results of the population pharmacokinetics analyses were to be presented in a separate report.

**Safety Results:**

***Summary of Adverse Events***

Treatment-emergent AEs were experienced by similar proportions of subjects in each treatment group, with a slightly higher proportion of subjects in the UK-369,003 50 mg MR group, and a slightly lower proportion in the UK-369,003 10 mg MR group (Table S4).

The most frequently reported all causality TEAEs were headache, dyspepsia, back pain, flushing, myalgia and diarrhea (Table S5). The most frequently reported TEAEs were experienced by similar proportions of subjects in each treatment group (<10%), and were all

considered treatment-related with the exception of back pain experienced by 3 subjects (2 subjects in the UK-369,003 100 mg MR group and 1 subject in the placebo group) and diarrhea experienced by 1 subject in the UK-369,003 100 mg MR group (Table S5). Headache was reported by more subjects in the UK-369,003 10 mg MR, 25 mg MR, 50 mg MR, 100 mg MR, 40 mg IR and tamsulosin 0.4 mg PR treatment groups, compared to placebo. Flushing was reported by more subjects in the UK-369,003 10 mg MR, 50 mg MR, 100 mg MR and 40 mg IR treatment groups, compared to placebo. Flushing was reported by fewer subjects in the UK-369,003 10 mg MR, 50 mg MR and 100 mg MR treatment groups compared to the UK-369,003 40 mg IR treatment group. Myalgia was reported by more subjects in the UK-369,003 10 mg MR, 50 mg MR, 100 mg MR and 40 mg IR treatment groups, compared to placebo, although the overall incidence was low.

**Table S4. Summary of Treatment-Emergent Adverse Events**

| | UK-369,003 | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **10 mg MR** | | **25 mg MR** | | **50 mg MR** | | **100 mg MR** | | **40 mg IR** | | **Tamsulosin 0.4 mg PR** | | **Placebo** | |
| Subjects evaluable for AEs | 53 | | 56 | | 53 | | 90 | | 89 | | 36 | | 38 | |
| | AC | TR | AC | TR | AC | TR | AC | TR | AC | TR | AC | TR | AC | TR |
| Number of AEs | 19 | 13 | 23 | 15 | 32 | 23 | 48 | 37 | 63 | 52 | 16 | 5 | 24 | 5 |
| Number (%) of subjects with: | | | | | | | | | | | | | | |
| AEs | 10 (18.9) | 10 (18.9) | 19 (33.9) | 13 (23.2) | 23 (43.4) | 16 (30.2) | 27 (30.0) | 20 (22.2) | 29 (32.6) | 26 (29.2) | 8 (22.2) | 3 (8.3) | 11 (28.9) | 5 (13.2) |
| SAEs | 1 (1.9) | 0 | 0 | 0 | 2 (3.8) | 0 | 2 (2.2) | 0 | 2 (2.2) | 0 | 1 (2.8) | 0 | 1 (2.6) | 0 |
| Severe AEs | 1 (1.9) | 0 | 1 (1.8) | 1 (1.8) | 2 (3.8) | 1 (1.9) | 5 (5.6) | 2 (2.2) | 3 (3.4) | 1 (1.1) | 0 | 0 | 0 | 0 |
| Discontinued due to AEs | 1 (1.9) | 1 (1.9) | 1 (1.8) | 1 (1.8) | 3 (5.7) | 2 (3.8) | 6 (6.7) | 4 (4.4) | 4 (4.5) | 4 (4.5) | 1 (2.8) | 0 | 0 | 0 |
| Dose reduced or temporarily discontinued due to AEs | 0 | 0 | 1 (1.8) | 0 | 3 (5.7) | 3 (5.7) | 1 (1.1) | 0 | 0 | 0 | 1 (2.8) | 0 | 0 | 0 |

MR=modified release; IR=immediate release; PR=prolonged release; AE=adverse event; AC=all causality; TR=treatment-related

## Table S5. Incidence of Treatment-Emergent Adverse Events[a] Reported in ≥2 Subjects in Any Treatment Group (Treatment-related in Parentheses)

| | 10 mg MR | | 25 mg MR | | UK-369,003 50 mg MR | | 100 mg MR | | 40 mg IR | | Tamsulosin 0.4 mg PR | | Placebo | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Subjects evaluable for AEs | 53 | | 56 | | 53 | | 90 | | 89 | | 36 | | 38 | |
| | AC | TR | AC | TR | AC | TR | AC | TR | AC | TR | AC | TR | AC | TR |
| Number of AEs | 19 | 13 | 23 | 15 | 32 | 23 | 48 | 37 | 63 | 52 | 16 | 5 | 24 | 5 |
| Number of subjects with AEs | 10 (18.9) | 10 (18.9) | 19 (33.9) | 13 (23.2) | 23 (43.4) | 16 (30.2) | 27 (30.0) | 20 (22.2) | 29 (32.6) | 26 (29.2) | 8 (22.2) | 3 (8.3) | 11 (28.9) | 5 (13.2) |
| Number (%) of subjects with MedDRA (v11.0) preferred term: | | | | | | | | | | | | | | |
| Headache | 5 (9.4) | 5 (9.4) | 2 (3.6) | 2 (3.6) | 4 (7.5) | 4 (7.5) | 5 (5.6) | 5 (5.6) | 5 (5.6) | 5 (5.6) | 2 (5.6) | 2 (5.6) | 1 (2.6) | 1 (2.6) |
| Dyspepsia | 1 (1.9) | 1 (1.9) | 1 (1.8) | 1 (1.8) | 4 (7.5) | 4 (7.5) | 3 (3.3) | 3 (3.3) | 3 (3.4) | 3 (3.4) | 0 | 0 | 1 (2.6) | 1 (2.6) |
| Back pain | 0 | 0 | 2 (3.6) | 2 (3.6) | 2 (3.8) | 2 (3.8) | 4 (4.4) | 3 (3.3) | 2 (2.2) | 2 (2.2) | 1 (2.8) | 1 (2.8) | 2 (5.3) | 0 |
| Flushing | 1 (1.9) | 1 (1.9) | 0 | 0 | 1 (1.9) | 1 (1.9) | 2 (2.2) | 2 (2.2) | 8 (9.0) | 8 (9.0) | 0 | 0 | 0 | 0 |
| Myalgia | 1 (1.9) | 1 (1.9) | 0 | 0 | 2 (3.8) | 2 (3.8) | 2 (2.2) | 2 (2.2) | 2 (2.2) | 2 (2.2) | 0 | 0 | 0 | 0 |
| Diarrhea | 1 (1.9) | 1 (1.9) | 0 | 0 | 1 (1.9) | 1 (1.9) | 2 (2.2) | 1 (1.1) | 1 (1.1) | 1 (1.1) | 1 (2.8) | 0 | 1 (2.6) | 1 (2.6) |
| Erythema | 1 (1.9) | 1 (1.9) | 0 | 0 | 1 (1.9) | 1 (1.9) | 2 (2.2) | 2 (2.2) | 2 (2.2) | 2 (2.2) | 0 | 0 | 0 | 0 |
| Arthralgia | 2 (3.8) | 1 (1.9) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.1) | 1 (1.1) | 1 (2.8) | 0 | 1 (2.6) | 0 |
| Dizziness | 0 | 0 | 0 | 0 | 1 (1.9) | 1 (1.9) | 1 (1.1) | 1 (1.1) | 2 (2.2) | 2 (2.2) | 0 | 0 | 1 (2.6) | 0 |
| Nasopharyngitis | 0 | 0 | 0 | 0 | 1 (1.9) | 0 | 1 (1.1) | 0 | 0 | 0 | 1 (2.8) | 0 | 2 (5.3) | 1 (2.6) |
| Abdominal pain upper | 0 | 0 | 0 | 0 | 1 (1.9) | 1 (1.9) | 1 (1.1) | 1 (1.1) | 2 (2.2) | 1 (1.1) | 0 | 0 | 0 | 0 |
| Dry mouth | 0 | 0 | 1 (1.8) | 1 (1.8) | 0 | 0 | 0 | 0 | 2 (2.2) | 2 (2.2) | 1 (2.8) | 1 (2.8) | 0 | 0 |
| Nausea | 0 | 0 | 1 (1.8) | 1 (1.8) | 0 | 0 | 2 (2.2) | 2 (2.2) | 0 | 0 | 0 | 0 | 0 | 0 |
| Dysuria | 0 | 0 | 2 (3.6) | 0 | 0 | 0 | 0 | 0 | 1 (1.1) | 0 | 0 | 0 | 0 | 0 |
| Rash | 0 | 0 | 0 | 0 | 0 | 0 | 1 (1.1) | 1 (1.1) | 2 (2.2) | 2 (2.2) | 0 | 0 | 0 | 0 |
| Angina pectoris | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.2) | 1 (1.1) | 0 | 0 | 0 | 0 | 0 | 0 |
| Abdominal discomfort | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (2.2) | 1 (1.1) | 0 | 0 | 0 | 0 |

MR=modified release; IR=immediate release; PR=prolonged release; AE=adverse event; AC=all causality; TR=treatment-related

[a] AEs that occurred in ≥2 subjects in any treatment group listed in ascending order according to total incidence

### *Discontinuations Due to Adverse Events*

Treatment-emergent AEs which led to discontinuation are detailed in Table S6.

**Table S6. Discontinuations Due to Adverse Events**

| Subject Age (years) | Adverse Event | Severity | Treatment Related | Outcome |
|---|---|---|---|---|
| **UK-369,003 10 mg MR** | | | | |
| 71 | Chest pain | Moderate | Yes | Ongoing |
| **UK-369,003 25 mg MR** | | | | |
| 68 | Headache | Severe | Yes | Resolved |
| **UK-369,003 50 mg MR** | | | | |
| 56 | Muscle spasms | Moderate | Yes | Resolved |
| 56 | Headache | Moderate | Yes | Resolved |
| 70 | Deep vein thrombosis[a] | Severe | No | Ongoing |
| **UK-369,003 100 mg MR** | | | | |
| 68 | Vitreous floaters | Severe | No | Unknown |
| 56 | Back pain | Moderate | Yes | Ongoing |
| | Musculoskeletal stiffness | Moderate | Yes | Ongoing |
| | Myalgia | Moderate | Yes | Resolved |
| | Skin exfoliation | Moderate | Yes | Resolved |
| | Flushing | Moderate | Yes | Ongoing |
| 65 | Angina pectoris[a] | Severe | No | Resolved |
| 70 | Nausea | Moderate | Yes | Resolved |
| | Fatigue | Mild | No | Resolved |
| | Nasopharyngitis | Mild | No | Resolved |
| 69 | Angina pectoris | Severe | Yes | Resolved |
| 62 | Back pain | Moderate | Yes | Resolved |
| **UK-369,003 40 mg IR** | | | | |
| 61 | Abnormal sensation in eye | Moderate | Yes | Resolved |
| 45 | Dizziness | Severe | Yes | Resolved |
| 58 | Abdominal pain upper | Moderate | Yes | Resolved |
| **Tamsulosin 0.4 mg PR** | | | | |
| 67 | Delusion[a] | Moderate | No | Resolved |

MR=modified release; IR=immediate release; PR=prolonged release; AE=adverse event
[a] Adverse event was a serious adverse event

### *Serious Adverse Events*

There were no deaths during the study. Treatment-emergent SAEs are detailed in Table S7.

**Table S7. Treatment-Emergent Serious Adverse Events**

| Subject Age (years) | Adverse Event | Severity | Treatment Related | Outcome |
|---|---|---|---|---|
| **UK-369,003 10 mg MR** | | | | |
| 71 | Abscess | Moderate | No | Ongoing |
| **UK-369,003 50 mg MR** | | | | |
| 70 | Erysipelas | Mild | No | Resolved |
| 70 | Deep vein thrombosis [a] | Severe | No | Ongoing |
| **UK-369,003 100 mg MR** | | | | |
| 65 | Angina pectoris[a] | Severe | No | Resolved |
| 74 | Thrombosis | Severe | No | Resolved |
| **UK-369,003 40 mg IR** | | | | |
| 61 | Pneumonia | Severe | No | Resolved |
| 57 | Intervertebral disc protrusion | Severe | No | Resolved |
| **Tamsulosin 0.4 mg PR** | | | | |
| 67 | Angina unstable | Moderate | No | Resolved |
| | Left ventricular failure | Moderate | No | Resolved |
| | Delusion[a] | Moderate | No | Resolved |
| **Placebo** | | | | |
| 60 | Aspiration bronchial | Moderate | No | Resolved |

MR=modified release; IR=immediate release
[a] Subject was discontinued for the adverse event

**CONCLUSION(S):** The objectives of this proof of concept study were successfully achieved. Reductions in both the $IPSS_{total}$ and IPSS storage and voiding subscores demonstrated efficacy for both storage and voiding LUTS. A dose response relationship was observed for and UK-369,003 50 mg MR and 100 mg MR showed efficacy of >2.5 points compared to placebo and >1 point compared to tamsulosin 0.4 mg PR.

Furthermore, an improvement in $Q_{max}$ was observed in the UK-369,003 100 mg MR and 40 mg IR treatment groups compared to placebo with a high posterior probability of UK-369,003 10 mg MR, 50 mg MR, and 100 mg MR being better than tamsulosin 0.4 mg PR. UK-369,003 was efficacious for IIEF-EF and QEQ across the dose range. There was no observable efficacy for over active bladder endpoints, although baselines for these variables were low in this BPH population. Patient reported outcome measures indicated a greater satisfaction, preference, and willingness to use again for the UK-369,003 50 mg MR and 100 mg MR treatment groups compared to placebo, UK-369,003 40 mg IR, and tamsulosin 0.4 mg PR.

Overall, UK-369,003 was efficacious in subjects with BPH with LUTS, and well tolerated across all doses with no apparent relationship between UK-369,003 dose and incidence or severity of AEs. The type and incidence of AEs reported in this study were similar to those observed with this class of compound and reported in previous studies with UK-369,003.