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COMPOUND NUMBER: UK-369,003

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Not Applicable

NCT NO.: NCT00479505

PROTOCOL NO.: A3711047

PROTOCOL TITLE: A Multi-Center, Randomized, Parallel Group, Double-blind, Placebo Controlled Estimation Study to Assess the Efficacy and Safety of Modified Release UK-369,003 in the Treatment of Men with Storage Lower Urinary Tract Symptoms (LUTS) With and Without Erectile Dysfunction (ED)

Study Center(s): 50 centers (Australia: 2 centers; Canada: 4 centers; Chile: 3 centers; Columbia: 2 centers; Finland: 5 centers; France: 5 centers; Germany: 5 centers; Greece: 2 centers: Italy: 3 centers; Latvia: 1 center; Norway: 2 centers; Poland: 6 centers; Slovakia: 4 centers; Spain: 1 center; Switzerland: 2 centers; United Kingdom: 3 centers)

Study Initiation and Completion Dates: 10 August 2007 to 20 June 2008

Phase of Development: Phase 2

Study Objective(s):

- Estimate the efficacy of UK-369,003 modified release (MR) versus placebo for the treatment of storage male LUTS with and without ED.
- To evaluate the safety and tolerability of UK-369,003 in men with storage LUTS with and without ED.
- Characterize the dose response relationship of UK-369,003 in men with storage LUTS with and without ED.

METHODS

Study Design: This was a multi-center, double-blind, placebo-controlled parallel group study in adult males with documented clinical diagnosis of over active bladder (OAB) as verified by the screening LUTS Diary.

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: with ED or without ED; with no more than 210 subjects in the LUTS with ED stratum and 150 subjects in the LUTS without ED stratum.

Number of Subjects (Planned and Analyzed): A total sample size of 300 subjects (60 subjects in the UK-369,003 10 mg MR, 25 mg MR, 50 mg MR, 100 mg MR and placebo treatment groups) was planned. Of the 480 subjects screened, 310 subjects completed screening and were randomized. Of the 310 randomized subjects, 309 were treated, and 307 subjects were included in the full analysis set (FAS), and 236 subjects were included in the per protocol analysis set (PPAS).

Diagnosis and Main Criteria for Inclusion: Subjects were male, aged ≥18 years with documented clinical diagnosis of OAB as verified by the screening LUTS Diary defined by: mean urinary frequency ≥8 times per 24 hours; mean number of urgency episodes, with or without urgency incontinence ≥1 episode per 24 hours; and mean voided volume <300 mL as verified by the bladder diary completed prior to randomization, and a maximum urine flow rate (Q_{max}) of >5 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 (CYP450) inhibitors, or warfarin were also excluded.

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

- UK-369,003 10 mg MR
- UK-369,003 25 mg MR

- UK-369,003 50 mg MR
- UK-369,003 100 mg MR
- placebo.

Study treatment was taken once daily between 11:00 and 13:00: 4 tablets were taken with water and swallowed whole without chewing, 1 after the other. For subjects on active treatment, 1 tablet corresponded to the active dose and the other 3 tablets were placebo tablets matching the other 3 doses; for subjects on placebo (and during the 2-week placebo run-in period) the 4 tablets were the matching placebo for each dose.

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

Efficacy Evaluations:

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).

International Prostate Symptom Score (IPSS)

Subjects were asked to complete the 1-week recall period version of the international prostate symptom score (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 international index of erectile function (IIEF), which comprise the erectile function (EF) domain, 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).

Over Active Bladder Questionnaire Short Form (OAB-q-SF)

Subjects were asked to complete the over active bladder questionnaire short form (OAB-q-SF) at baseline, Week 4, and end of treatment (Week 12)/early withdrawal (Visits 3, 6 and 7/early withdrawal).

Patient Perception of Bladder Condition (PPBC)

Subjects were asked to complete the patient perception bladder condition (PPBC) at baseline and Weeks 2, 4 and end of treatment (Week 12)/early withdrawal (Visits 3, 5, 6 and 7/early withdrawal).

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

Subjects were asked to complete the international consultation on incontinence questionnaire-male lower urinary tract symptoms (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).

Patient Reported Treatment Impact (PRTI) Questionnaire

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

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 following measures were derived from the LUTS Diary:

- Percentage and absolute change in micturition frequency after 2, 4 and 12 weeks of double-blind treatment.
- Change in mean volume voided per micturition after 2, 4 and 12 weeks double-blind treatment.
- Percentage and absolute change in urgency episode 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.

- 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 normalized micturition frequency (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 incontinence episode frequency (IEF) after 2, 4 and 12 weeks of double-blind treatment.

Each of the above efficacy endpoints were analyzed for the full analysis set (FAS) using a mixed effect model with repeated measures. From the model, least squares (LS) means for each treatment the treatment differences between UK-369,003 MR doses and placebo, and the associated two-sided 90% confidence intervals (CIs) at each on-treatment time point were estimated.

In addition, the time point-by-treatment interaction term was fitted to generate the appropriate LS means and the associated two-sided 90% CIs for the change from baseline for each treatment and on-treatment time point, adjusted for the baseline value and ED status. Contrasts for each dose of UK-369,003 MR against placebo were generated from the same model to provide the required differences in LS means and the associated two-sided 90% CIs. As the purpose of this study was estimation, no p-values were presented. As this is an exploratory study, no adjustments were made to the two-sided 90% CIs to allow for multiplicity of efficacy endpoints.

Secondary Efficacy Endpoints

<u>International Prostate Symptom Score (IPSS)</u>

The following were calculated:

- The international prostate symptom score ($IPSS_{total}$): the sum of the scores of non-missing items of the IPSS Questions 1 to 7.

- The IPSS storage subscore: sum of the scores of non-missing items of the IPSS Questions 2, 4 and 7.

- The IPSS voiding subscore: sum of the score of non-missing items of the IPSS Questions 1, 3, 5 and 6.

The following efficacy endpoints were derived:

- The change in the IPSS total score from baseline to the subsequent visits

- The change in the IPSS storage sub-score from baseline to the subsequent visits
- The change in the IPSS voiding sub-score from baseline to the subsequent visits.

The IPSS endpoints were analyzed for the FAS ($IPSS_{total}$) and per protocol analysis set (PPAS) ($IPSS_{total}$, IPSS storage and voiding subscores) in a similar way as for the primary endpoint.

Descriptive statistics, based on the FAS, were provided for the individual questions of the IPSS (Questions 1 to 7 and the quality of life question).

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

The IIEF-EF was calculated as the sum of the IIEF Questions 1-5 and 15.

The IIEF-EF was analyzed and summarized, based on the FAS, in a similar way as for the primary endpoint.

The IIEF was summarized for the ED subgroup.

Quality of Erection Questionnaire (QEQ)

The QEQ was calculated as the sum of the QEQ Questions 5 and 6.

The QEQ was analyzed and summarized, based on the FAS, in a similar way as for the primary endpoint.

The QEQ was summarized for the ED subgroup.

Over Active Bladder Questionnaire Short From (OAB-q-SF)

The following were calculated:

- Subject perception of urinary symptoms bother.
- Subject perception of health related quality of life (HRQL).

The symptom bother scale score was calculated as the transformed sum of the individual scores.

The subject perception of HRQL scale score was calculated as the transformed sum of the individual scores.

The OAB-q-SF endpoints were analyzed and summarized, based on the FAS, in a similar way as for the primary endpoint.

Patient Perception of Bladder Condition (PPBC)

The PPBC was analyzed, based on the FAS, using a proportional odds logistic regression model with terms for treatment and ED status. The treatment differences for UK-369,003 MR doses versus placebo were estimated by odds ratios with two-sided 90% CIs. The observed proportions of each level of response were presented for each treatment group for overall LUTS with ED and without ED.

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

Individual questions were summarized, based on the FAS, by treatment and visit. Descriptive statistics and plots were produced.

Patient Reported Treatment Impact Questionnaire (PRTI)

The 5-level responses to questions 1, 3 and 4 were analyzed, base on the FAS, using a proportional odds logistic regression model with terms for treatment and ED status. The treatment differences for UK-369,003 MR doses versus placebo were estimated with two-sided 90% CIs. The observed proportions of each level of response were presented for each treatment group. Question 2 asked which treatment was received for the urinary problem before the study. The data were listed by 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 480 subjects screened, 310 subjects completed screening and were randomized to 1 of 5 treatment groups (Table S1). A total of 280 subjects completed the study, and 28 subjects discontinued: 5 subjects (8.3%), 6 subjects (10.5%), 4 subjects (5.9%) and 8 subjects (12.7%) in the UK-369,003 10 mg MR, 25 mg MR, 50 mg MR and 100 mg MR groups, respectively, and 5 subjects (7.9%) in the placebo group. Of the 310 randomized subjects, 309 were treated and 307 were included in the FAS, and 236 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

	UK-369,003				Placebo
	10 mg MR	**25 mg MR**	**50 mg MR**	**100 mg MR**	
Number (%) of subjects					
Randomized	60	57	67	63	63
Treated	59[a]	57	67	64[b]	62[a]
Completed	54 (91.5)	51 (89.5)	63 (94.0)	55 (85.9)	57 (91.9)
Discontinued	5 (8.5)	6 (10.5)	4 (6.0)	9 (4.1)	5 (8.1)
AE	3 (5.1)	4 (7.1)	2 (3.0)	6 (9.4)	2 (3.2)
Protocol deviation	0	0	0	1 (1.6)	0
Other	0	0	1 (1.5)	3 (4.7)	1 (1.6)
No longer willing to participate	2 (3.4)	2 (3.5)	1 (1.5)	0	2 (3.2)
Analyzed for efficacy					
FAS	59 (100.0)	57 (100.0)	67 (100.0)	62[c] (96.9)[a]	62 (100.0)
PPAS	42 (71.2)	48 (84.2)	51 (76.1)	47 (73.4)	48 (77.4)
Analyzed for safety					
AEs	59 (100.0)	57 (100.0)	67 (100.0)	64 (100.0)	62 (100.0)
Laboratory data	55 (93.2)	53 (94.7)	63 (94.0)	57 (89.1)	59 (95.2)

MR=modified release; AE=adverse event; FAS=full analysis set; PPAS=per protocol analysis set

[a] Excludes 2 subjects who were randomized in error (Subjects 10571001 and 10911003)

[b] Includes 1 subject (Subject 10561001) treated in the single-blind run-in period

[c] Excludes 1 subject who did not attend a follow-up visit (Subject 10281007) and 1 subject (10561001) treated in the single-blind run-in period

Table S2. Demography

	UK-369,003				Placebo
	10 mg MR	**25 mg MR**	**50 mg MR**	**100 mg MR**	
Number of subjects	59	57	67	64	62
Mean age (SD), years	60.2 (10.4)	59.8 (9.7)	60.1 (8.4)	59.3 (11.0)	60.5 (9.6)
Race,					
White	53	52	59	58	57
Other	6	5	8	6	5
Weight (SD), kg	82.4 (12.9)	83.5 (12.8)	86.0 (15.7)	80.0 (10.7)	85.4 (14.8)
Height (SD), cm	172.9 (6.5)	174.4 (7.7)	174.2 (7.3)	172.5 (6.4)	173.3 (6.5)

MR=modified release; SD=standard deviation

Table S3. Mean (SD) Efficacy Endpoints at Baseline

	UK-369,003				Placebo
	10 mg MR	**25 mg MR**	**50 mg MR**	**100 mg MR**	
Number of subjects	55	54	64	60	61
Mean voided volume per micturition	180.4 (52.59)	174.7 (53.30)	191.1 (43.65)	180.1 (46.63)	188.6 (49.62)
Micturition frequency per 24 hours	10.8 (2.43)	11.3 (2.65)	10.6 (2.27)	10.5 (2.40)	10.5 (2.05)
Urgency episode frequency per 24 hours	9.3 (3.42)	9.6 (3.93)	8.3 (3.71)	8.8 (3.49)	8.4 (3.56)
Number of subjects	51	52	58	58	58
Nocturnal frequency	1.8 (0.94)	2.0 (1.20)	1.7 (1.04)	1.5 (1.00)	1.8 (1.17)
Number of subjects	58	57	66	62	62
$IPSS_{total}$	14.7 (5.53)	15.4 (6.86)	15.1 (5.43)	14.3 (6.08)	14.8 (7.21)

MR=modified release; SD=standard deviation; $IPSS_{total}$=international prostate symptom score (total)

Efficacy Results: ***Primary Evaluations***

There was no apparent treatment effect, with similarly small changes observed for each LUTS Diary endpoint across all treatment groups (including placebo) at all weeks. For micturition frequency, mean differences over placebo ranged from 0.25 (worsening) to -0.51 (improvement), mean differences over placebo for mean voided volume ranged from -4.23 mL (improvement) to 14.01 mL (worsening) and for urgency episode frequency, mean differences from placebo ranged from 0.40 (improvement) to -0.98 (worsening). Although dose response modeling was carried out using E_{max} models for micturition frequency, mean voided volume, urgency episode frequency, nocturnal frequency and incontinence episode frequency, the models were variable and results not robust. Given there was no apparent treatment effect with UK-369,003, additional analyses were not undertaken to characterize any dose-response relationship.

Secondary Evaluations

$IPSS_{total}$

From repeated measures analysis the adjusted mean change from baseline results showed small changes in $IPSS_{total}$ for all treatment groups at Weeks 1, 2, 4 and 12. Mean differences from placebo ranged from 0.31 to -2.25 points and the largest decreases from placebo were observed at Weeks 1 and 12 for the UK-369,003 50 mg MR treatment group.

IPSS Storage Subscore

Change from baseline results showed decreases in IPSS storage subscore for all treatment groups at Weeks 1, 2, 4 and 12. However, with the exception of UK-369,003 50 mg MR, the reported decreases with UK-369,003 were small with no apparent trend across time or dose (mean differences from placebo ranged from 0.65 to -0.80 points).

IPSS Voiding Subscore.

From repeated measures analysis, adjusted mean change from baseline results showed decreases in IPSS voiding subscore for all treatment groups at Weeks 1, 2, 4 and 12. The UK-369,003 treatment groups performed better than placebo at all weeks, although, with the exception of the UK-369,003 50 mg MR treatment group, the decreases were small with no apparent trend across time or dose (mean differences from placebo ranged from 0.40 to -1.43 points).

IPSS Individual Questions

For the individual questions that contribute to the storage and voiding subscales, and ultimately $IPSS_{total}$, there were no observable differences between treatment groups for mean absolute and change-from-baseline scores for the IPSS individual questions.

At Week 12, decreases were observed for all treatment groups in the Quality of Life (QoL) score (maximum decrease=1.2 points in the UK-369,003 50 mg MR treatment group). No apparent treatment effect was seen for any of the UK--369,003 doses compared to placebo.

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

For all subjects (ie, subjects with and without ED), raw mean baseline values ranged from 15.0 to 18.0 points across all treatment groups. Raw mean change from baseline results showed increases (improvements) in IIEF-EF for all treatment groups at Weeks 4 and 12 with larger increases in the UK-369,003 treatment groups (ranging from 2.1 to 7.0 points) compared to placebo (ranging from 0.5 to 1.3 points). For the subset of subjects with ED, mean baseline values were similar across UK-369,003 treatment groups (15.4 to 20.3 points), with the lowest score (indicating more severe subjects) observed in the placebo treatment group (14.2 points). Repeated measures analysis on this subgroup (subjects with ED) showed that mean change from baseline scores were greater in all UK-369,003 treatment groups compared to placebo (mean differences from placebo range from 0.88 to 6.01 points).

Quality of Erection Questionnaire (QEQ)

For all subjects (ie, subjects with and without ED), mean baseline values were comparable across all treatment groups (5.6 to 6.4 points). Change from baseline results showed decreases (improvements) in QEQ score for all treatment groups at Weeks 4 and 12 which were smaller in the placebo treatment group (UK-369,003 treatment group responses range from -0.6 to -2.2 points and maximum response in the placebo treatment group was -0.5 points). For the subgroup of subjects with ED, at Weeks 4 and 12, raw changes from baseline were larger than those in the overall population (both subjects with and without ED). Repeated measures analysis demonstrated that all UK-369,003 treatment groups resulted in a greater decrease (improvement) in QEQ score than observed with placebo at both Weeks 4 and 12 (differences from placebo range from -0.10 to -2.29 points).

Over Active Bladder Questionnaire Short Form (OAB-q-SF)

Change from baseline results showed improvements in bother scores for all treatment groups at Weeks 4 and 12. At Weeks 4 and 12, small improvements versus placebo were observed for the UK-369,003 10 mg MR, 50 mg MR and 100 mg MR treatment groups (mean differences from placebo range from -0.62 to -6.19 points). Change from baseline results showed improvements in HRQL for all treatment groups at Weeks 4 and 12. At Week 12, small improvements compared to placebo were observed for all UK-369,003 treatment groups (mean differences from placebo at Week 12 ranged from 0.70 to 1.71 points).

Patient Perception of Bladder Condition (PPBC)

At Week 12, ‘some minor problems’ was the category for most subjects for all treatment groups with the exception of the UK-369,003 10 mg MR treatment group for which most subjects were in the category ‘some moderate problems’. A repeatedly measured ordinal analysis was done to estimate treatment differences showing that at Week 12, subjects in the UK-369,003 25 mg MR, 50 mg MR and 100 mg MR treatment groups were less likely than placebo-treated subjects to report problems with their bladder condition (odds ratios of 1.94, 2.08 and 1.55, respectively).

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

Across domains (storage, voiding and post micturition), changes of small magnitude in both frequency and bother scores were seen in all treatment groups at Week 4 and Week 12. There was no difference between the changes seen with UK-360,003 doses and placebo.

Patient Reported Treatment Impact Questionnaire (PRTI)

With the exception of UK-369,003 10 mg MR treated-subjects for preference and willingness to reuse, and 100 mg MR-treated subjects for preference, subjects were more likely to report greater satisfaction, preference and willingness to reuse UK-369,003 compared to placebo. Satisfaction, preference, and willingness to use UK-369,003 were greatest in the UK-369,003 50 mg MR treatment group (odds ratios of 1.77, 1.57 and 1.69, respectively).

Pharmacokinetic, Pharmacodynamic, and/or Other Results:

Future anonymized pharmacogenomic analyses will be presented in a separate report. Results of the population pharmacokinetics analyses will be presented in a separate report.

Safety Results:

During the study there was no apparent effect on laboratory parameters, mean changes in vital signs or PVR urine volume across time with dose.

Summary of Adverse Events

Treatment-emergent AEs (TEAEs) were experienced by similar proportions of subjects in the UK-369,003 10 mg MR and placebo treatment groups, with a slightly higher proportion of subjects reporting and AE in the UK-369,003 25 mg, 50 mg and 100 mg MR treatment groups (Table S4).

The most frequently reported all causality TEAEs were headache (8.1% of subjects), and back pain (7.8% of subjects) (Table S5). Headache was reported by more subjects in the UK-369,003 10 mg MR, 50 mg MR and 100 mg MR treatment groups, compared to placebo (maximum 11.9% of subjects in the UK-369,003 10 mg MR group compared to 6.5% of subjects in the placebo group and 3.5% in the UK-369,003 25 MR group). Back pain was reported by more subjects in the UK-369,003 50 mg MR and 100 mg MR treatment groups (7.5% and 7.8% of subjects, respectively) compared to the UK-369,003 10 mg MR, 25 mg MR and placebo treatment groups (1.7%, 1.8% and 3.2%, respectively). Myalgia was reported by more subjects in the UK-369,003 25 mg MR, 50 mg MR and 100 mg MR treatment groups, compared to placebo (maximum 10.4% in the UK-369,003 50 mg MR group compared to no subjects in the placebo group), although the overall incidence was low.

Table S4. Summary of Treatment-Emergent Adverse Events

	UK-369,003								Placebo	
	10 mg MR		25 mg MR		50 mg MR		100 mg MR			
Subjects evaluable for AEs	59		57		67		64		62	
	AC	TR	AC	TR	AC	TR	AC	TR	AC	TR
Number of AEs	42	18	47	36	53	24	61	31	42	22
Number (%) of subjects with:										
AEs	22 (37.3)	10 (16.9)	23 (40.4)	17 (29.8)	32 (47.8)	18 (26.9)	31 (48.4)	22 (34.4)	22 (35.5)	10 (16.1)
SAEs	3 (5.1)	0	0	0	0	0	2 (3.1)	0	0	0
Severe AEs	4 (6.8)	1 (1.7)	3 (5.3)	3 (5.3)	1 (1.5)	0	3 (4.7)	2 (3.1)	0	0
Discontinued due to AEs	3 (5.1)	1 (1.7)	4 (7.0)	3 (5.3)	2 (3.0)	1 (1.5)	6 (9.4)	5 (7.8)	2 (3.2)	2 (3.2)
Dose reduced or temporarily discontinued due to AEs	2 (3.4)	1 (1.7)	2 (3.5)	1 (1.8)	0	0	1 (1.6)	1 (1.6)	2 (3.2)	2 (3.2)

MR=modified release; AE=adverse event; AC=all causality; TR=treatment-related; SAE=serious adverse event

Table S5. Incidence of Treatment-Emergent Adverse Events Reported in ≥2 Subjects in Any Treatment Group

	UK-369,003								Placebo	
	10 mg MR		25 mg MR		50 mg MR		100 mg MR			
Subjects evaluable for AEs										
	AC	TR	AC	TR	AC	TR	AC	TR	AC	TR
Number of AEs	42	18	47	36	53	24	61	31	42	22
Number of subjects with AEs	22 (37.3)	10 (16.9)	23 (40.4)	17 (29.8)	32 (47.8)	18 (26.9)	31 (48.4)	22 (34.4)	22 (35.5)	10 (16.1)
Number (%) of subjects with MedDRA (v11.0) preferred term[a]:										
Headache	7 (11.9)	4 (6.8)	2 (3.5)	2 (3.5)	5 (7.5)	4 (6.0)	7 (10.9)	7 (10.9)	4 (6.5)	4 (6.5)
Back pain	1 (1.7)	1 (1.7)	1 (1.8)	1 (1.8)	5 (7.5)	4 (6.0)	5 (7.8)	1 (1.6)	2 (3.2)	1 (1.6)
Dyspepsia	0	0	1 (1.8)	1 (1.8)	6 (9.0)	3 (4.5)	3 (4.7)	2 (3.1)	3 (4.8)	2 (3.2)
Myalgia	0	0	2 (3.5)	2 (3.5)	7 (10.4)	7 (10.4)	5 (7.8)	4 (6.3)	0	0
Nasopharyngitis	1 (1.7)	0	1 (1.8)	0	3 (4.5)	0	1 (1.6)	0	2 (3.2)	1 (1.6)
Diarrhea	0	0	2 (3.5)	2 (3.5)	1 (1.5)	0	3 (4.7)	2 (3.1)	0	0
Dizziness	2 (3.4)	2 (3.4)	1 (1.8)	1 (1.8)	0	0	3 (4.7)	2 (3.1)	0	0
Tinnitus	1 (1.7)	1 (1.7)	2 (3.5)	2 (3.5)	2 (3.0)	0	1 (1.6)	0	0	0
Flushing	1 (1.7)	1 (1.7)	1 (1.8)	1 (1.8)	0	0	2 (3.1)	2 (3.1)	1 (1.6)	1 (1.6)
Pain in extremity	1 (1.7)	1 (1.7)	0	0	1 (1.5)	1 (1.5)	2 (3.1)	0		0
Rhinitis	1 (1.7)	1 (1.7)	0	0	2 (3.0)	0	0	0	0	0
Influenza	1 (1.7)	0	0	0	1 (1.5)	0	0	0	2 (3.2)	0
Nausea	0	0	0	0	0	0	2 (3.1)	2 (3.1)	1 (1.6)	1 (1.6)
Fatigue	0	0	0	0	0	0	1 (1.6)	1 (1.6)	2 (3.2)	2 (3.2)
Abdominal pain upper	2 (3.4)	0	1 (1.8)	1 (1.8)	0	0	0	0	0	0
Hypertension	0	0	1 (1.8)	1 (1.8)	0	0	0	0	2 (3.2)	0
Constipation	0	0	0	0	0	0	2 (3.1)	1 (1.6)	0	0
Vomiting	0	0	0	0	0	0	2 (3.1)	1 (1.6)	0	0
Chest discomfort	0	0	0	0	0	0	2 (3.1)	1 (1.6)	0	0
Muscle Spasms	0	0	0	0	2 (3.0)	1 (1.5)	0	0	0	0
Rhinitis allergic	0	0	2 (3.5)	1 (1.8)	0	0	0	0	0	0

MR=modified 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				
64	Tinnitus	Severe	Yes	Resolved
48	Myocardial infarction[a]	Severe	No	Resolved
59	Palpitations	Mild	No	Still Present
UK-369,003 25 mg MR				
73	Dizziness	Severe	Yes	Resolved
54	Hypertension	Severe	Yes	Still Present
63	Eye Pain	Mild	No	Resolved
	Haemorrhoids	Mild	No	Resolved
47	Rash Papular	Mild	Yes	Resolved
UK-369,003 50 mg MR				
60	Myalgia	Mild	Yes	Resolved
61	Vitreous haemorrhage	Mild	No	Resolved
UK-369,003 100 mg MR				
47	Headache	Severe	Yes	Resolved
59	Asthenia	Severe	Yes	Resolved
	Fatigue	Severe	Yes	Resolved
	Dizziness	Moderate	Yes	Resolved
60	Back Pain	Moderate	Yes	Resolved
64	Myalgia	Mild	Yes	Resolved
75	Gastric Ulcer[a]	Moderate	No	Still Present
	Mallory-weiss[a] syndrome	Moderate	No	Still Present
56	Headache	Moderate	Yes	Resolved
Placebo				
71	Angina pectoris	Mild	Yes	Resolved
64	Fatigue	Moderate	Yes	Resolved
	Polyuria	Mild	Yes	Resolved

MR=modified release
MedDra v11.0 coding dictionary applied
[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				
45	Patella fracture	Mild	No	Recovering
69	Abdominal pain upper	Severe	No	Recovered
48	Myocardial infarction[a]	Severe	No	Recovered
UK-369,003 100 mg MR				
64	Abdominal pain lower	Severe	No	Recovered
	Acute abdomen	Severe	No	Recovered
75	Mallory-Weiss syndrome[a]	Moderate	No	Recovered
	Gastric ulcer[a]	Moderate	No	Recovered

MR=modified release
MedDra v11.0 coding dictionary applied
[a] Subject was discontinued for the adverse event

CONCLUSIONS: Overall there were no clinically relevant treatment differences observed in micturition frequency, mean voided volume, urgency episode frequency, or nocturnal frequency endpoints for any dose of UK-369,003 compared to placebo, with no evidence of efficacy for UK-369,003 in the treatment of male storage LUTS.

Decreases compared to placebo were observed in $IPSS_{total}$ and IPSS storage and voiding subscores for the UK-369,003 50 mg MR treatment group only. For the IPSS QoL question, there was no apparent treatment effect across UK-369,003 dose groups compared to placebo.

UK-369,003 was efficacious for IIEF and QEQ in all subjects (ie, subjects with and without ED) compared to placebo.

Subjects reported a greater satisfaction, preference and willingness to reuse UK-369,003 compared to placebo; with subjects in the UK-390,003 treatment group reporting greatest satisfaction, preference and willingness to use again.

Overall, the disease-specific scales, ICIQ-MLUTS and OAB-q-SF, did not show any treatment effect for UK-369,003 compared to placebo, indicative of no treatment benefit on storage LUTS and OAB patient-reported symptom impact. The PPBC and PRTI scales showed treatment benefit for UK-369,003 compared to placebo, indicative of an overall patient-perceived benefit for their urinary condition.

The incidence of SAEs was low across treatment groups, with no SAEs assessed by the investigator, or sponsor, as related to study treatment. The type and incidence of AEs reported in this study were similar to those observed in previous studies conducted with UK-369,003 with headache, back pain and myalgia the most commonly reported AEs with greater incidence for subjects receiving UK-369,003 compared to placebo. Overall, the incidences of treatment emergent and treatment-related AEs, and AEs leading to discontinuation were low across all UK-369,003 treatment groups.

Overall, UK-369,003 MR did not appear efficacious in the treatment of male storage LUTS but was well-tolerated across the dose range as evidence through the low incidences of AEs and discontinuations from the study.