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COMPOUND NUMBER: UK-369,003

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:

NCT NO.: NCT00408954

PROTOCOL NO.: A3711045

PROTOCOL TITLE: A Multi-Center, Randomized, Cross-Over, Double-Blind, Third Party Open, Placebo Controlled, Pilot Study to Assess the Urodynamic Effects of Modified Release UK-369,003 in Men With Lower Urinary Tract Symptoms (LUTS)

Study Centers: 11 centers in Europe (Slovakia, Czech Republic and the Netherlands)

Study Initiation and Completion Dates: 13 March 2007 to 13 June 2008

Phase of Development: Phase 2

Study Objectives:

- A pilot study to assess the urodynamic changes induced by 100 mg UK-369,003 modified release (MR) formulation versus placebo in men with LUTS.
- Assess the safety and tolerability of UK-369,003 in men with LUTS.

METHODS

Study Design: This was a multi-center double blind, randomized, placebo-controlled, third party open, crossover, Phase 2 pilot study with 2 treatment sequences, conducted in 31 male subjects with LUTS.

For each subject, the study comprised 6 visits: screening (Visit 1), baseline/start of Period 1 (Visit 2), end of Period 1 (Visit 3), start of Period 2 (Visit 4), end of Period 2 (Visit 5) and follow-up (Visit 6).

After screening and following a washout period of up to 4 weeks, subjects had a baseline assessment of their bladder storage and voiding function. They were then randomized (1:1 ratio) to 1 of the 2 treatment sequences: 100 mg UK-369,003 MR followed by placebo, or placebo followed by 100 mg UK-369,003 MR. Each of the treatments was administered once daily (QD) for a minimum of 2 weeks. At the end of Period 1, subjects had an end of treatment period (EOT1) pressure flow study assessment, followed by a washout period of 2-4 weeks (exact length was at the investigator's discretion). At the beginning of Period 2

(BOT2) subjects attended the clinic to receive medication and complete patient outcome measures but did not undergo any urodynamic assessments. After receiving the second study treatment, an end of treatment period (EOT2) pressure flow study assessment was conducted. A follow-up visit occurred 1 week after the EOT2; in the absence of any adverse events (AEs) this visit could be conducted by telephone.

An interim analysis was conducted in order to assess variability of emerging data with the aim of potential sample size re-estimation. The analysis did not support stopping the study early and the original sample size was retained. Confidence intervals (CIs) of the final analysis were not adjusted post-interim due to the exploratory nature of this study. The results of these analyses were not intended to enable individuals directly involved in the execution of the study (such as the investigators, sponsor's operational team and central urodynamics reader) to identify treatment assignments for subjects until after the study was completed.

Number of Subjects (Planned and Analyzed): It was planned to recruit sufficient subjects so that 20 subjects completed the study. It was expected to recruit a minimum of 50% subjects with DO. Of the 97 subjects screened, 31 subjects completed screening and were randomized to a treatment sequence (UK-369,003/Placebo or Placebo/UK-369,003).

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 at screening. Subjects were also required to have a urodynamically defined bladder outlet obstruction based on bladder outlet obstruction index (BOOI, formerly Abrams-Griffiths [AG] number) >40, at baseline. A minimum of 50% of the population were also to have urodynamically confirmed detrusor overactivity (DO).

Study Treatment: During Periods 1 and 2, subjects self-administered 2 x 50 mg tablets of UK-369,003 MR or placebo in a single oral dose for 14 days according to the randomization schedule. Each tablet was to be swallowed whole, without chewing, with a glass of ambient temperature water. UK-369,003 was supplied by the sponsor as 50 mg MR blue and white, round bilayer tablets and matching placebo tablets.

Efficacy Evaluations: Urodynamic assessments were performed according to the International Continence Society recommendations. All centers measured the following endpoints: detrusor pressure at maximum flow rate ($P_{det}Q_{max}$), average detrusor pressure during micturition, maximum urine flow rate (Q_{max}), average flow rate (Q_{ave}), cystometric capacity, post-void residual (PVR) urine volume, BOOI, bladder contractility index (BCI), bladder voiding efficiency (BE), volume at first unstable contraction, frequency and mean amplitude of unstable contractions (where they occurred) and voided volume.

Patient Reported Outcomes Research Evaluations:

International Prostate Symptom Score (IPSS): Subjects were asked to complete the 1-week recall period version of the IPSS at screening and at Visits 2 to 5, to assess and evaluate the

severity of their LUTS. Subjects who discontinued the study early were asked to complete the questionnaire at their follow-up visit.

Patient Reported Treatment Impact (PRTI): Subjects were asked to complete the PRTI at Visits 3 and 5. Subjects who discontinued the study early were asked to complete the questionnaire at their follow-up visit.

Safety Evaluations: Adverse events (AEs) were monitored throughout the study. Hematology and biochemistry test were performed at screening and Visits 3 and 5. Urinalysis was performed at screening and Visits 2, 3, 4 and 5. HbA_{1c} was measured at screening, if indicated. A prostate-specific antigen (PSA) test was performed at screening unless the results of a PSA test performed within the last 3 months were available. Vital sign measurements were taken at screening and Visits 2, 3, 4 and 5. A single 12-lead electrocardiogram (ECG) was obtained from each subject at screening.

Statistical Methods: The primary analysis was based on the Full Analysis Set (FAS) without missing data imputed, and change from baseline in the urodynamic efficacy parameters listed in the efficacy evaluations section. Change from baseline was analyzed using a general linear model (analysis of variance [ANOVA]), and PROC MIXED in SAS with terms in the model for subject, treatment, and period. The subject effect was fitted as a random effect and the treatment and period effects were fitted as fixed effects. Restricted Maximum Likelihood estimates for the treatment difference (UK-369,003 100 mg MR minus placebo), the associated standard error and 2-sided 80% CIs were calculated. No p-values were presented.

To explore the robustness of the analysis and to check for the presence of a sequence effect, the analysis was repeated with a term for sequence added to the ANOVA model as a fixed effect; the subject effect was then nested within the sequence effect as a random effect. If less than half the subjects had missing data for 1 of 2 periods, the treatment effect would still be estimated using PROC MIXED for a crossover design, utilizing between subject information. If more than half the subjects have missing data for 1 of 2 periods, an ANOVA model for a parallel group design with terms for treatment and baseline would be used for non-missing data. The assumptions of the final model were checked by investigation of the residuals. If the errors were not normally distributed, a non-parametric method of analysis would be used to generate the CIs. In this case, the analysis would be based on the PPAS.

For each urodynamic endpoint, summary statistics were provided by treatment group. If a minimum of 4 subjects had urodynamically confirmed DO, the summary statistics and plots for each urodynamic endpoint would be provided by treatment group and subjects with and without DO.

Summary statistics were produced for the IPSS total score, the IPSS sub-scores and the changes from the baseline by treatment group. In addition, for exploratory purposes, the score and the change from baseline (assessed for each period) for each of individual IPSS Questions 1 to 7 and the quality of life question was summarized by treatment. The association between the urodynamic endpoints and the IPSS was examined based on the FAS.

The binary endpoints derived from the 3 PRTI questions were analyzed based on the FAS using a non-linear mixed model (NLMIXED) to fit a random version of logistic regression. For each of the 3 PRTI questions, summary tables for the derived binary, and the original 5-level response were produced by treatment in the FAS.

RESULTS

Subject Disposition and Demography: Of the 97 subjects screened, 31 subjects completed screening and were randomized to a treatment sequence (Table S1). All subjects received at least the first of their allocated treatments. Two subjects were discontinued from the study due to AEs during Period 1 (1 subject under UK-369,003 100 mg and 1 subject under placebo) and did not receive the second treatment. One additional subject was discontinued from the study during Period 2 (UK-369,003 100 mg) due to an AE. This subject received both treatments, although UK-369,003 treatment (Period 2) was not completed.

One subject receiving placebo had a reduction in the number of tablets (to 1 tablet QD) due to AEs of palpitations (2 separate events) and increased blood pressure.

Table S1. Subject Evaluation Groups

Number of Subjects	100 mg UK-369,003 MR	Placebo
Screened (N=97)		
Completed Screening & Assigned Treatment (N=31)		
Treated	30	30
Completed	28	29
Discontinued[a]	2	1
Analyzed for Efficacy		
Full Analysis Set	29	29
Per Protocol Analysis Set	24	24
Restricted Per Protocol Analysis Set	23	23
Analyzed for Safety (Safety Analysis Set)		
Adverse Events	30	30
Laboratory Data	29	29

[a] All discontinuations were due to AEs

All subjects were white males. Demographic characteristics are presented in Table S2. Approximately half (48%) of the subjects had a urodynamically confirmed DO.

Table S2. Subject Demography

	All Subjects
Number of Subjects	31
Age, years	
Mean (SD)	60.7 (9.2)
Range	45 – 78
BMI, kg/m^2	
Mean (SD)	26.6 (4.0)
Range	18.4 – 36.2

SD = Standard deviation, BMI = Body mass index

Efficacy Results: The primary efficacy endpoints were the changes from baseline in urodynamic parameters at Visits 3 and 5 (Table S3 and Table S4). Least squares means showed that 100 mg UK-369,003 MR had little effect on urodynamic endpoints related to bladder filling function; there were no marked differences when compared to placebo. Among the urodynamic endpoints related to bladder voiding function, only PVR volume showed a treatment difference for which CIs did not overlap with zero; PVR volume was decreased following treatment with 100 mg UK-369,003 MR but increased with placebo treatment (difference -13.16 mL [80% CI: -21.89, -4.43]). Average and maximum detrusor pressures both decreased with placebo and to a greater extent with 100 mg UK-369,003 MR, with the CIs of the treatment differences overlapping with zero.

Q_{max} was marginally decreased following treatment with 100 mg UK-369,003 MR but not placebo. Average flow rate was slightly increased to a similar extent on both treatments, and there was no treatment difference in voided volume.

BCI decreased following treatment with placebo and to a greater extent with 100 mg UK-369,003 MR. BOOI was similarly decreased, although the treatment difference had somewhat wider CIs. BE decreased slightly with 100 mg UK-369,003 MR, with wide CIs associated with the treatment difference.

Results of analyses based on the PPAS and RPPAS were supportive of those based on the FAS. Sensitivity analyses showed no evidence of a significant treatment sequence effect.

Table S3. Mean (SD) Changes from Baseline in Urodynamic Endpoints – FAS

	100 mg UK-369,003 MR		Placebo	
	Visit 3[a] n=15[c]	Visit 5[b] n=15	Visit 3[a] n=14	Visit 5[b] n=14
Urodynamic Voiding Endpoints				
Q_{max} (mL/sec)	-1.3 (2.3)	1.1 (2.9)	0.4 (2.6)	0.2 (3.2)
Q_{ave} (mL/sec)	-0.5 (1.3)	0.8 (1.7)	0.4 (1.8)	-0.1 (1.6)
$P_{det}Q_{max}$[c] (cmH_2O)	-3.0 (16.3)	-11.4 (16.7)	-4.7 (19.2)	-5.6 (15.1)
Average detrusor pressure during micturition[c] (cmH_2O)	-2.9 (23.7)	-11.1 (13.9)	-4.9 (12.5)	-2.4 (21.2)
PVR volume (mL)	-5.4 (57.2)	-16.0 (32.7)	-3.9 (31.9)	9.9 (62.7)
Bladder outlet obstruction index[c]	-0.3 (17.4)	-13.5 (20.0)	-5.4 (20.5)	-6.0 (18.7)
Bladder contractility index[c]	-9.8 (19.5)	-6.0 (16.4)	-2.9 (21.8)	-4.5 (17.0)
Bladder voiding efficiency (%)	-6.0 (26.5)	5.4 (15.4)	5.0 (22..6)	-0.5 (29.1)
Voided volume (mL)	7.7 (72.8)	13.8 (114.4)	39.3 (93.8)	-20.0 (69.1)
Urodynamic Filling Endpoints				
Cystometric capacity (mL)	24.7 (72.9)	-3.9 (114.0)	30.8 (69.1)	-18.3 (68.3)
Volume at first unstable detrusor contraction (mL)	-32.7 (131.2)	29.5 (159.1)	28.0 (80.4)	-64.6 (163.8)
Frequency of unstable contractions[c]	0.7 (2.2)	-1.4 (2.4)	-0.5 (2.4)	0.2 (3.1)
Mean amplitude of unstable contractions[c] (cmH_2O)	9.5 (18.7)	-5.2 (12.7)	-0.6 (11.5)	-2.8 (19.0)

n = Number of subjects included in analysis, SD = Standard deviation, Q_{max} = Maximum urine flow rate, Q_{ave} = Average flow rate, $P_{det}Q_{max}$ = Detrusor pressure at maximum flow rate, PVR = Post-void residual

[a] End of Period 1

[b] End of Period 2

[c] n=14 at Visit 3 (UK-369,003) for: $P_{det}Q_{max}$, average detrusor pressure during micturition, BOOI, BCI, frequency of unstable contractions, mean amplitude of unstable contractions

Table S4. Summary of ANOVA Analyses for Urodynamic Endpoints Treatment Differences – FAS

	Number of Subjects in Analysis		LS Mean (SE)		Difference (UK-369,003-Placebo)	
	100 mg UK-369,003 MR	Placebo	100 mg UK-369,003 MR	Placebo	Estimate	80% CI
Urodynamic Voiding Endpoints						
Q_{max} (mL/sec)	28	28	-0.15 (0.525)	0.23 (0.524)	-0.38	(-0.99, 0.23)
Q_{ave} (mL/sec)	28	28	0.12 (0.306)	0.11 (0.306)	0.01	(-0.35, 0.38)
$P_{det}Q_{max}$ (cmH_2O)	27	28	-7.84 (3.167)	-4.99 (3.132)	-2.86	(-6.42, 0.71)
Average detrusor pressure during micturition (cmH_2O)	27	28	-7.23 (3.485)	-3.49 (3.443)	-3.75	(-7.87, 0.38)
PVR volume (mL)	28	28	-9.76 (8.962)	3.40 (8.956)	-13.16	(-12.89, -4.43)
BOOI	27	28	-7.62 (3.599)	-5.42 (3.565)	-2.20	(-5.85, 1.45)
Bladder contractility index	27	28	-8.39 (3.557)	-3.79 (3.502)	-4.60	(-9.59, 0.40)
BE (%)	28	28	-0.48 (4.541)	1.84 (4.536)	-2.32	(-8.10, 3.46)
Voided volume (mL)	28	28	9.95 (16.717)	7.08 (16.701)	2.87	(-17.57, 23.31)
Urodynamic Filling Endpoints						
Cystometric capacity (mL)	28	28	10.11 (15.251)	5.80 (15.236)	4.32	(-15.27, 23.91)
Volume at first unstable detrusor contraction (mL)	28	28	-3.68 (26.273)	-18.27 (26.250)	14.59	(-16.28, 45.47)
Frequency of unstable contractions	27	28	-0.31 (0.511)	-0.14 (0.502)	-0.16	(-0.94, 0.61)
Mean amplitude of unstable contractions (cmH_2O)	27	28	2.13 (3.099)	-1.71 (3.039)	3.84	(-1.47,9.15)

SE = Standard error, CI = Confidence interval, Q_{max} = Maximum urine flow rate, Q_{ave} = Average flow rate, $P_{det}Q_{max}$ = Detrusor pressure at maximum flow rate, PVR = Post-void residual, BOOI = Bladder outlet obstruction index, BE = Bladder voiding efficiency

The same statistical analysis was repeated on the study population stratified by DO status. Cystometric capacity in subjects with urodynamically confirmed DO was increased to a greater extent with 100 mg UK-369,003 MR than with placebo (treatment difference 27.37 mL [80% CI: -3.91, 58.64]). The mean amplitude of unstable contractions increased slightly on UK-369,003 and decreased on placebo (treatment difference 17.25 cmH_2O [80% CI: 7.70, 26.80]. In contrast, BE decreased slightly on UK-369,003 and increased on placebo (treatment difference -7.95% [80% CI: -15.69, -0.20]); although the clinical impact of this change was negligible.

For subjects without DO, 100 mg UK-369,003 MR led to a greater reduction in $P_{det}Q_{max}$, average detrusor pressure during micturition, BCI and BOOI than the effect achieved on placebo. Small increases were observed in Q_{max} and BE for both treatments. The small sample size and relatively wide CIs associated with the treatment differences should be considered when interpreting these data.

Patient Reported Outcomes Research Results: For IPSS parameters, mean values were decreased from baseline to a significantly greater extent with 100 mg UK-369,003 MR compared to placebo, at Visit 3 and Visit 5 (Table S5).

Table S5. Summary of ANOVA Analyses for IPSS Treatment Differences – FAS

	Number of Subjects in Analysis		LS Mean (SE)		Difference (UK-369,003-Placebo)	
	100 mg UK-369,003 MR	Placebo	100 mg UK-369,003 MR	Placebo	Estimate	80% CI
Total Score	29	28	-6.3 (1.0)	-2.8 (1.0)	-3.5	(-5.3, -1.7)
Storage Sub-Score	29	28	-2.4 (0.4)	-0.9 (0.4)	-1.5	(-2.3, -0.7)
Voiding Sub-Score	29	28	-3.9 (0.6)	-1.9 (0.7)	-2.0	(-3.2, -0.9)

SE = Standard error

The statistical analyses for the PRTI endpoints indicated a trend towards treatment preference with UK-369,003. The odds ratios (80% CI) for treatment with 100 mg UK-369,003 MR compared to treatment with placebo ranged from 1.22 (0.57, 2.62) for subject willingness to re-use the treatment (Question 3) to 1.58 (0.66, 3.77) for subject global satisfaction with treatment (Question 1).

Safety Results: There were no deaths or other serious AEs during this study. Treatment-emergent AEs which led to discontinuation were experienced by 3 subjects: 2 subjects receiving 100 mg UK-369,003 MR (treatment-related myalgia and non-treatment-related depressed mood) and 1 subject receiving placebo (treatment-related dizziness). All events resolved and none were considered serious by the investigator. One subject receiving placebo had a reduction in dose (to 1 tablet QD) due to AEs of palpitations (2 separate events) and increased blood pressure; all events resolved without corrective therapy.

The most commonly reported all causality and treatment-related AE was headache, which was reported by 3 subjects in each treatment group. Other AEs reported by ≥2 subjects in either treatment group were dyspepsia, flushing, bronchitis, myalgia and micturition urgency (Table S6). All other AEs were reported by no more than 1 subject in either treatment group. With the exception of the 3 AEs which led to subject discontinuation, all AEs were considered mild or moderate in intensity.

Table S6. Incidence of Most Commonly Reported[a] Treatment Emergent Adverse Events

Number of subjects with MedDRA (v11.0) preferred term:	100 mg UK-369,003 MR		Placebo	
	All Causalities N=30	Treatment-Related N=30	All Causalities N=30	Treatment-Related N=30
Headache	3	3	3	3
Dyspepsia	2	2	0	0
Flushing	2	2	1	1
Bronchitis	2	0	0	0
Myalgia	2	2	0	0
Micturition urgency	2	1	0	0

AE = Adverse event, MedDRA = Medical Dictionary for Regulatory Activities
[a] Reported by at least 2 subjects in either treatment group

Eight subjects experienced laboratory abnormalities from normal baseline and 3 subjects experienced laboratory abnormalities from abnormal baseline. No laboratory abnormalities were recorded as AEs. There were no clinically significant changes in vital signs.

CONCLUSIONS: In this population of men with LUTS associated with BPH, differences were observed between 100 mg UK-369,003 MR and placebo on the following voiding urodynamic endpoints: PVR volume, $P_{det}Q_{max}$ and average detrusor pressure during micturition, as well as BCI, and BOOI, for which the upper 80% CI narrowly crossed zero.

A reduction was observed with 100 mg UK-369,003 MR compared to placebo in PVR volume, with a beneficial effect of 100 mg UK-369,003 MR on bladder voiding urodynamic endpoints, as evidenced through a lowering of $P_{det}Q_{max}$ and average detrusor pressure during micturition with little change in Q_{max} and Q_{ave}, suggestive of potential decrease in urethral pressure. BE was increased on placebo and slightly reduced by 100 mg UK-369,003 MR, albeit with wide CIs. However, the clinical relevance of BE and BCI reductions was offset by the reduction in PVR volume seen with 100 mg UK-369,003 MR compared to placebo.

The beneficial treatment effects of UK-369,003 observed on voiding parameters were more evident in subjects without DO. These effects included decreases in maximum and average detrusor pressure, decreases in PVR volume, BOOI and BCI, and small increases in Q_{max} and BE. For subjects with present DO, this was not observed, however cystometric capacity increased with 100 mg UK-369,003 MR and to a greater extent than with placebo. Increase of mean amplitude of unstable contractions in this sub-group was offset by an increase in a volume of first unstable contraction; however, the clinical impact of the latter changes was negligible.

Results of analyses based on the PPAS and RPPAS were supportive of those based on the FAS.

A clinically and statistically significant treatment effect was observed for IPSS endpoints, but not for PRTI endpoints.

AEs reported during the course of the study were similar to those observed in previous studies conducted with UK-369,003 with headache, dyspepsia, myalgia and flushing the most commonly reported AEs in subjects receiving 100 mg UK-369,003 MR. Overall, the incidences of treatment emergent and treatment-related AEs, and AEs leading to discontinuation were low, with 100 mg UK-369,003 MR being well tolerated in this population.