A Randomized Trial of Modified-Release Versus Immediate-Release Tolvaptan in ADPKD

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Introduction: Tolvaptan, for treatment of autosomal dominant polycystic kidney disease (ADPKD), is provided as immediate-release (IR) tablets administered twice daily in split-dose regimens to suppress urine osmolality to <300 mOsm/kg. A modified-release (MR) formulation was developed for once-daily (QD) dosing to increase compliance and mitigate urinary symptom burden. This phase 2, dose-ranging study (NCT01210560) compared pharmacokinetics, pharmacodynamics, and tolerability of several MR regimens with IR in patients with ADPKD.

Methods: This was a multicenter, parallel-arm, randomized, crossover, double-blind, placebo-controlled trial. Each of 2 study arms had 12 subjects and 3 crossover periods. Dose regimens were administered for 7 days; placebo-masked QD versus split-dose treatments. Endpoints included pharmacokinetic parameters, percentage of subjects with urine osmolality <300 mOsm/kg, urine volume, number of daily urine voids, and tolerability.

Results: Tolvaptan MR 20 to 120 mg exhibited dose-proportional pharmacokinetics. Percentage of subjects with spot urine osmolality <300 mOsm/kg increased with dose, with tolvaptan MR 120 mg and IR 90+30 mg each suppressing 91.7% of subjects below this level. Urinary burden on the ADPKD Nocturia Quality of Life, ADPKD Urinary Urgency, and ADPKD Urinary Frequency Questionnaires correlated with tolvaptan exposure, with high interindividual variability in responses. Changes in questionnaire scores were sensitive to changes in urine volume but not proportional to volume change, reflecting differences in subject tolerance to increased urine volume.

Conclusion: Tolvaptan MR exhibited predictable and dose-proportional pharmacokinetics and no improvement in tolerability versus tolvaptan IR. Tolerability of the urinary effects of treatment within the high-dose MR and IR groups exhibited substantial interindividual variability.

ADPKD is a systemic disorder characterized by kidney cysts and gradual kidney enlargement. The antidiuretic hormone arginine vasopressin (AVP) contributes to ADPKD pathogenesis by increasing the production of cyclic adenosine 3′-5′-monophosphate in the kidney, which in turn promotes cyst growth.[1–3] Inhibition of the AVP V2 receptor decreases intracellular cyclic adenosine 3′-5′-monophosphate.[4] Clinically, the AVP V2-receptor antagonist tolvaptan has been shown to reduce the rates of kidney growth and functional decline in ADPKD.[5] Tolerability to tolvaptan is limited by aquaretic adverse events (AEs) (e.g., thirst, polyuria, pollakiuria, nocturia) resulting from suppression of AVP antidiuretic activity; in addition, clinically significant elevation of liver enzymes has been observed in approximately 5% of patients with

ADPKD taking tolvaptan.[5] In the TEMPO 3:4 study, 23% of subjects in the tolvaptan arm discontinued from the trial; the most common reason for discontinuation was AE (67% of discontinuations), with approximately half of discontinuations due to AEs resulting from aquaretic AEs.[5]

In clinical use, tolvaptan is administered as IR tablets in split-dose regimens; the higher morning dose (45, 60, or 90 mg) is followed 8 to 9 hours later by a lower dose (15 or 30 mg). This regimen is designed to produce maximal suppression of urine osmolality during the day with tapering of concentrations to maintain urine osmolality at <300 mOsm/kg overnight but with minimal nocturia. A QD, MR formulation of tolvaptan was developed, as patients are more compliant with dosing on QD regimens.[6] In addition, it was expected that more gradual tolvaptan absorption might reduce the incidence of aquaretic AEs. The present phase 2, dose-ranging trial (NCT01210560) was conducted to compare the pharmacokinetics (PK), pharmacodynamics (PD), and tolerability of multiple doses of tolvaptan MR (20 mg QD, 60 mg QD, 120 mg QD and 20+20 mg) versus tolvaptan IR (90+30 mg) in subjects with ADPKD.

METHODS

Ethical Conduct
This trial was conducted under the investigational new drug exemption of the U.S. Food and Drug Administration and in compliance with Good Clinical Practice, the sponsor's standard operating procedures, and ethical principles for the protection of human research subjects that have their origins in the Declaration of Helsinki. The study protocol and informed consent form were reviewed and approved by the institutional review board or independent ethics committee for each investigational site before the commencement of the trial. Written informed consent was obtained from all subjects.

Trial Design
This was a phase 2, multicenter, parallel-arm ($n = 12$/arm), randomized, crossover, double-blind, and placebo-controlled trial in subjects with ADPKD (Figure 1). In a 3-period crossover, dose regimens were administered for 7 days, including placebo to mask QD versus split-dose treatments. In Arm 1, subjects received a 90+30 mg split dose of tolvaptan IR (IR 90+30 mg); a 120-mg QD dose of tolvaptan MR (MR, 120 mg); and, in incomplete block randomization, either tolvaptan MR 20 mg QD (MR, 20 mg), 60 mg QD (MR, 60 mg), or 20 mg in a split dose (MR, 20+20 mg). Arm 2 subjects received tolvaptan MR 20 mg QD, tolvaptan MR 60 mg QD, and tolvaptan MR 20+20 mg in a randomized crossover design. PK, PD, and tolerability

assessments were conducted for 24 hours following the seventh dose. At the conclusion of their final treatment period, subjects were asked to rank their treatments (week 1, 2, or 3) for overall tolerability. Seven days after the last dose, a follow-up phone call for determination of new AEs was conducted.

Between days −22 and −7, subjects underwent initial screening, which included baseline assessments for daily number of urine voids during the day and at night (daily diaries for a minimum of 5 days were to be recorded), and for exploratory purposes only, urinary symptom burden questionnaires.

At the end of the screening period, subjects were to check into the clinic on day −2 for 24 hours to obtain baseline PD assessments (beginning on day −1) for urine volume and urine osmolality for 24 hours, and for spot osmolality at 0.5 hour before dosing on day 1 after withholding fluids for 6 hours. Except for the first dose of each period and the doses taken in the clinic on the last day of each regimen, all other doses were taken by the subject as an outpatient to allow determination of the tolerability and compliance with tolvaptan dosing in a subject's daily routine. Subjects were asked to drink to thirst during the outpatient dosing days and to limit dietary salt <5 g/d, dietary protein <1 g/kg per day and caffeinated drinks/foods to no more than 2 coffee equivalents per day.

Study Population
This trial enrolled adults age 18 to 50 years with ADPKD as assessed by modified Ravine criteria,[7] and with estimated glomerular filtration rate (eGFR) >60 ml/min per 1.73 m^2 calculated by the 4-variable Modification of Diet in Renal Disease equation.[8] Subjects were excluded if they had used diuretics within the past 14 days; cytochrome P450 3A4 inhibitors, with the exception of amiodarone, within 30 days; or cytochrome P450 3A4 inducers within 7 days of dosing. Other reasons for exclusion included incontinence, overactive bladder, urinary retention (e.g., benign prostatic hypertrophy), or significant nocturia/urgency (outside of the 2 to 4 times awakening per night expected for subjects with ADPKD). Subjects were also excluded if they had liver disease, liver function abnormalities (other than Gilbert's disease), or serology other than that expected for ADPKD with cystic liver disease (i.e., normal except for possible alterations in alkaline phosphatase and gamma-glutamyl transferase).

Rationale for Treatment Selection
Dosing for 7 days was chosen because previous trials have indicated that within this time frame, tolvaptan IR and MR concentrations should be at steady state for both PK and PD. Tolvaptan IR 90+30 mg as a split dose
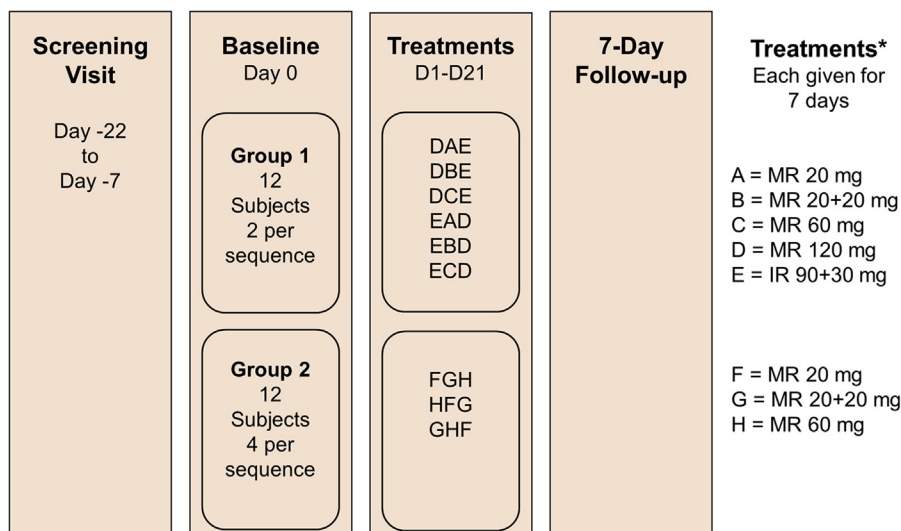
Figure 1. Study design. *Doses were administered at approximately 0800 and 1600 hours. Placebo capsules and tablets were used to mask split dosing versus once-daily dosing. D, day; IR, immediate release; MR, modified release.

and MR 120 mg QD were chosen because higher doses of tolvaptan are associated with an increasing incidence of pollakiuria and nocturia; therefore, these dose levels were expected to show the greatest sensitivity if changes in the underlying PK profile improved tolerability. Testing of tolvaptan MR 20 mg, 60 mg, and 120 mg QD provided a broad range of tolvaptan exposure, allowing characterization of a wide exposure-response relationship. Finally, testing of tolvaptan MR 20+20 mg (first dose in the morning with second dose ∼8 hours later to match IR split-dose regimen) would demonstrate whether tolerability and nighttime urinary suppression of osmolality were improved relative to an increased QD dose (i.e., comparison with the 60 mg QD regimen).

Before dosing on day 0, subjects were assigned to a treatment sequence in a randomized, double-blinded fashion via an interactive response technology according to a computer-generated randomization scheme provided by the biostatistics department of the sponsor. In group 1, subjects were randomized in blocks of 6, and in group 2, blocks of 3.

Placebo tablets and capsules, identical in appearance, were used to ensure masking of IR versus MR formulation, so that knowledge of doses and/or regimens did not affect the diary and patient-reported outcome responses. Each subject received an identical number of tablets and capsules regardless of the dose group assignment.

Endpoints
Pharmacokinetics
On the seventh day of dosing for each regimen, the following PK parameters were determined for tolvaptan: maximum (peak) plasma concentration (C_{max}),

minimum (trough) plasma concentration (C_{min}), average plasma concentration during the dosing interval at steady state, time to maximum (peak) plasma concentration, area under the concentration-time curve (AUC) from time 0 to 24 hours postdose (AUC_{0-24h}) and, for QD regimens, apparent total body clearance from plasma following extravascular administration.

Pharmacodynamics
The main PD outcome was the number of subjects with a spot urine osmolality concentration <300 mOsm/kg at 23.5 hours postdose, an indicator of continuous AVP suppression in the kidney. Additional PD measures were duration that urine osmolality remained <300 mOsm/kg, urine osmolality AUC_{0-24h}, urine volume and osmolality for the intervals of 0 to 4, 4 to 8, 8 to 12, 12 to 16, and 16 to 24 hours, and 0 to 24-hour urine volume.

Tolerability
For each treatment period, tolerability of each treatment regimen was evaluated with respect to the number of urine voids during daytime and nighttime, as well as impact of urinary symptoms on a subject's daily life using questionnaires on urinary urgency, urinary frequency, and nocturia. At conclusion of their trial participation, subjects were asked to rank treatments by tolerability.

Prior research has established that patients with ADPKD are affected by urinary symptoms, specifically urinary urgency, urinary frequency, and nocturia, which in turn lead to social and emotional impacts.[9] However, evaluation of questionnaires commonly used to assess urinary symptoms and their impact, for example, the Nocturia International Consultation on Incontinence Modular Questionnaire-Nocturia[10] and

Table 1. Exploratory questionnaires to evaluate patient urinary burden

Questionnaire	Questions	Dimensions assessed	Scoring
ADPKD Nocturia Quality-of-Life Questionnaire	Q1–Q11	Burden of nocturia (concentration, energy, fatigue, productivity, worry, level of bother)	0–4 each 0–44 total ↑ score = ↓ burden
	Q12	Interference of nocturia with daily life	0–10 ↑ score = ↑ interference
ADPKD Urinary Urgency Questionnaire	Q1	Presence of urinary urgency	Yes/No
	Q2–Q6	Burden of urinary urgency (frequency of urgency, severity and level of bother from urgency)	0–4 each 0–20 total[a] ↑ score = ↑ burden
	Q7–Q14	Impact of urinary urgency on life (chores, physical activities, relationships, leisure activities, travel/commuting, social activities, emotional state)	0–4 each 0–32 total ↑ score = ↑ impact
ADPKD Urinary Frequency Questionnaire	Q1	Presence of urinary frequency	Yes/No
	Q2	Burden of urinary frequency (level of bother)	0–4 ↑ score = ↑ bother
	Q3–Q10	Impact of urinary frequency on life (chores, physical activities, relationships, leisure activities, travel/commuting, social activities, emotional state)	0–4 each 0–32 total ↑ score = ↑ impact

↑, increasing; ↓, decreasing; ADPKD, autosomal dominant polycystic kidney disease.
[a]Question 6 (on the amount of time urgency is present in an average 24-h period) is asked only at screening; therefore, the range for total burden of urgency score in this study was 0–16.

the Urgency, Severity, and Impact Questionnaire,[11] showed limited applicability to how patients with ADPKD describe their symptoms and impacts. This resulted in the creation of the ADPKD Nocturia Quality-of-Life Questionnaire, ADPKD Urinary Urgency Questionnaire, and ADPKD Urinary Frequency Questionnaire, which were not validated and only used in this single study. These interim questionnaires formed the basis for development of the individual domains of the ADPKD Urinary Impact Scale, a quality-of-life assessment instrument used in subsequent clinical studies (NOCTURNE, OVERTURE).[12–14]

The ADPKD Nocturia Quality-of-Life Questionnaire consists of 12 questions that measure the impact of having to get up at night to urinate in concepts related to concentration, energy, fatigue, productivity, worry, interference with activities, and level of bother (Table 1). The ADPKD Urinary Urgency Questionnaire consists of 14 questions that assess for the presence of urinary urgency, severity of and level of bother from urinary urgency, as well as the impact of urinary urgency on the subject's life (chores, physical activities, relationships, leisure activities, travel/commuting, social activities, emotional state). The ADPKD Urinary Frequency Questionnaire comprises 10 questions that assess for the presence of urinary frequency, the level of bother from urinary frequency, and the impact of urinary frequency on the subject's life (chores, physical activities, relationships, leisure activities, travel/commuting, social activities, emotional state).

Safety
Safety endpoints included treatment-emergent AEs (TEAEs) and clinical laboratory parameters. Heart rate

and blood pressure after subjects remained supine ≥3 minutes were also assessed.

Bioanalytical Methods
Plasma concentrations of tolvaptan were analyzed using reversed-phase high-performance liquid chromatography with tandem mass spectrometric detection as described previously.[15] Briefly, tolvaptan and an internal standard were extracted from 250 μl heparinized plasma using solid phase extraction. Calibration standards prepared in plasma and extracted along with samples were used to quantitate the concentrations by weighted ($1/x^2$) linear regression of peak area ratios of analyte-to-internal standard. Quality control samples were evaluated during validation to assess performance of the method and resulted in a percent coefficient of variation of ≤9.2% and relative error between −4.5 and 2.0%. Plasma analysis was performed at ICON Bioanalytical Laboratories (Whitesboro, NY).

Pharmacokinetic Analyses
Plasma PK parameters for tolvaptan were determined using actual blood-sample times in all calculations. Values of C_{max} and time to maximum (peak) plasma concentration were determined directly from the observed data. Values of AUC were estimated using the linear trapezoidal rule. Values of apparent total body clearance from plasma following extravascular administration were determined as dose/$AUC_{0–24h}$/body weight. PK parameter calculations were performed using WinNonlin Pro (version 5.2; Pharsight Corporation, Mountain View, CA).

Statistical Analyses
The number of subjects per group (12) was chosen based on the PK and PD variability observed in

Table 2. Demographics and baseline clinical characteristics

Characteristic, statistic	Group 1 ($n = 12$)	Group 2 ($n = 13$)	Total ($n = 25$)
Gender, n (%)			
Male	5 (41.7)	9 (69.2)	14 (56.0)
Female	7 (58.3)	4 (30.8)	11 (44.0)
Race, n (%)			
White	12 (100)	13 (100)	25 (100)
Age, yr			
Mean (SD)	39.4 (4.3)	36.8 (9.0)	38.0 (7.1)
Range	32–49	21–50	21–50
Height, cm			
Mean (SD)	176.3 (11.0)	177.4 (11.2)	176.9 (10.9)
Range	162–201	154–197	154–201
Weight, kg			
Mean (SD)	80.4 (17.4)	82.2 (18.9)	81.3 (17.9)
Range	61–111	60–118	60–118
Age at PKD diagnosis[a]			
Mean (SD)	26.1 (8.0)	28.0 (7.1)	27.1 (7.4)
Range	14–39	12–40	12–40
eGFR MDRD-4			
Mean (SD)	76.7 (16.8)	75.9 (14.5)	76.3 (15.3)
Range	57–111	50–98	50–111
History of hypertension[a]			
n (%) responding "yes"	7 (58.3)	9 (69.2)	16 (64.0)
History of proteinuria[a]			
n (%) responding "yes"	5 (41.7)	2 (15.4)	7 (28.0)
History of liver cysts[a]			
n (%) responding "yes"	11 (91.7)	7 (53.8)	18 (72.0)

eGFR MDRD-4, estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease 4-variable equation; PKD, polycystic kidney disease.
[a]Medical histories were based on patient reports.

previous studies. This number of subjects per cohort was considered adequate to generate an indication of tolerability. The trial was not sized for statistical comparisons of PK, PD, or tolerability parameters.

Analyses were based on the intent-to-treat population observed cases dataset within the treatment period. The analysis of PK included only subjects having valid measurements, and analysis of PD included all subjects who took at least 1 dose of study drug and had measurements of the PD endpoint. The analysis of safety included all subjects who took at least 1 dose of study drug.

Safety variables were summarized by dose group. A TEAE was defined as an AE that started after initiation of study drug, or if the event was continuous from baseline and was serious, study drug-related, or resulted in death, discontinuation, or interruption or reduction of the study drug.

RESULTS

Subject Characteristics and Disposition
A total of 30 subjects were screened and 25 subjects were randomized and treated; all 25 treated subjects completed the trial. One more subject than planned was randomized in group 2 as a replacement subject due to a protocol deviation. The study was conducted at 6

trial centers in the United States, with enrollment starting in October 2010 and the study completion date in June 2011.

Demographic and baseline clinical characteristics were generally similar between groups 1 and 2 (Table 2). The mean (SD) age of ADPKD diagnosis was 26.1 (8.0) years in group 1 and 28.0 (7.1) years in group 2. The ADPKD diagnosis was confirmed radiographically in all subjects. Most subjects (64.0%) reported a history of hypertension, although the percentage was not as high as in the TEMPO 3:4 (79.4%) or REPRISE (93.0%) studies of tolvaptan.[5,16]

Pharmacokinetics
Figure 2 shows the median plasma tolvaptan concentration versus time profile for tolvaptan MR 20 mg, MR 20+20 mg, MR 60 mg, MR 120 mg, and IR 90+30 mg following administration on day 7. A summary of tolvaptan PK parameters for each dosage regimen is presented in Table 3.

The MR 20 mg, MR 60 mg, and MR 120 mg regimens exhibited dose-proportional increases in AUC_{0-24h} and average plasma concentration during the dosing interval at steady state with increasing dose. However, increases in C_{max} were less than dose-proportional and increases in C_{min} were larger than expected with increasing dose. For MR 120 mg compared with IR 90+30 mg, tolvaptan C_{max} was approximately 10% lower but AUC_{0-24h} was approximately 1.2-fold higher and C_{min} 2.4-fold higher. C_{min} for MR 60 mg and MR 20+20 mg were similar. Median time to maximum (peak) plasma concentration values for MR doses occurred at approximately 6 hours compared with 2 hours for IR 90+30 mg.

Pharmacodynamics
Urine osmolality showed a decreasing trend with increasing tolvaptan dose. The percentage of subjects with spot urine osmolality <300 mOsm/kg following 7 days of treatment increased as tolvaptan dose increased: 29.4% for MR 20 mg, 56.3% for MR 60 mg, 68.8% for MR 20+20 mg, and 91.7% for both MR 120 mg and IR 90+30 mg (Figure 3). The median time that urine osmolality remained <300 mOsm/kg was 16 hours for tolvaptan MR 20 mg and 24 hours for all other regimens (Figure 4).

Urinary Burden
The mean 24-hour urine volume on treatment showed a trend to increase with tolvaptan dose, with values ranging from approximately 4750 ml for tolvaptan MR 20 mg to 7400 ml for tolvaptan MR 120 mg and IR 90+30 mg (Figure 5a). The mean number of urine voids during the day and at night reflected this trend, with small changes from baseline observed for tolvaptan MR
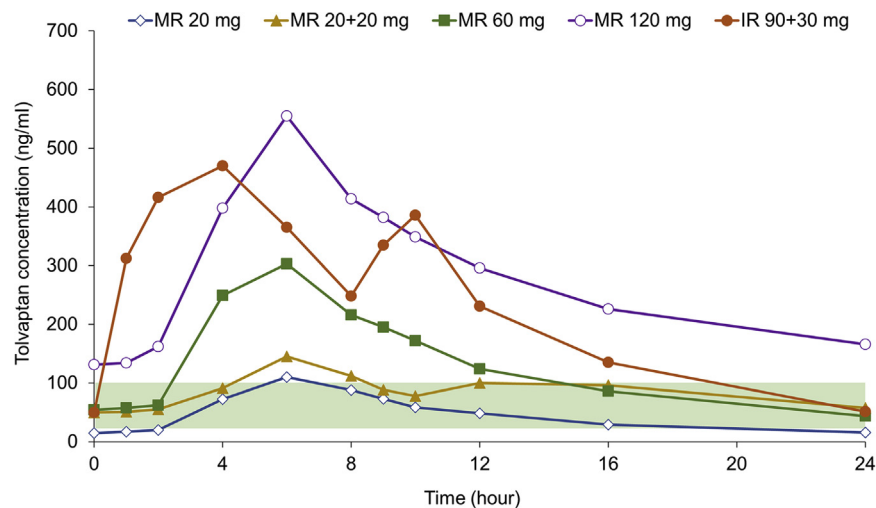
Figure 2. Median plasma tolvaptan concentration-time curves on day 7 of tolvaptan treatment for 5 different dosage regimens in subjects with autosomal dominant polycystic kidney disease. Green box indicates range of tolvaptan concentrations that are minimally effective to maximally saturating for increasing urine excretion rate.[17] IR, immediate release; MR, modified release.

20 mg and greater increases for tolvaptan MR 120 mg and IR 90+30 mg (Figures 5b, 6b).

The reported patient burden due to nocturia on the Nocturia Quality-of-Life Questionnaire at baseline was a mean of 41 points on a 0- to 44-point scale, where higher scores indicate lower burden. During treatment, reported patient burden due to nocturia increased as mean scores decreased, by 1.5 points for MR 20 mg, 6.9 points for MR 20+20 mg, 5.1 points for MR 60 mg, 15.0 points for MR 120 mg, and 13.1 points for IR 90+30 mg. In contrast to scoring of the burden due to nocturia, interference with daily life by nocturia was evaluated with higher scores indicating greater interference (range, 0–10). At baseline, subjects did not report nocturia-related interference (mean scores ≤0.5). For tolvaptan MR 120 mg and IR 90+30 mg, the mean scores increased to 4.6 and 4.1, respectively, whereas the mean scores for the other dose groups ranged from 1.1 to 2.5, a trend that reflected the mean number of nighttime urine voids (Figure 6a and b).

At baseline, approximately 20% of subjects reported that they were experiencing urinary urgency, and approximately 30% of subjects reported experiencing urinary frequency as assessed on the ADPKD Urinary Urgency Questionnaire and ADPKD Urinary Frequency Questionnaire, respectively. At the end of treatment, the percentage of subjects reporting urinary urgency increased to 47% for MR 20 mg, 77% for MR 20+20 mg, 71% for MR 60 mg, 83% for tolvaptan MR 120 mg, and 92% for IR 90+30 mg. The percentage of subjects reporting urinary frequency at the end of treatment increased to 59% for MR 20 mg, 88% for MR 20+20 mg, 94% for MR 60 mg, and 100% for both tolvaptan MR 120 mg and IR 90+30 mg.

The patient-reported symptom burden due to urinary urgency at baseline was a mean of 1.5 points on a 0 to 16 point scale, and the patient-reported impact due to urinary urgency was a mean of 0.5 on a 0 to 32 point scale, with higher scores indicating higher burden or impact on both scales. During treatment, reported
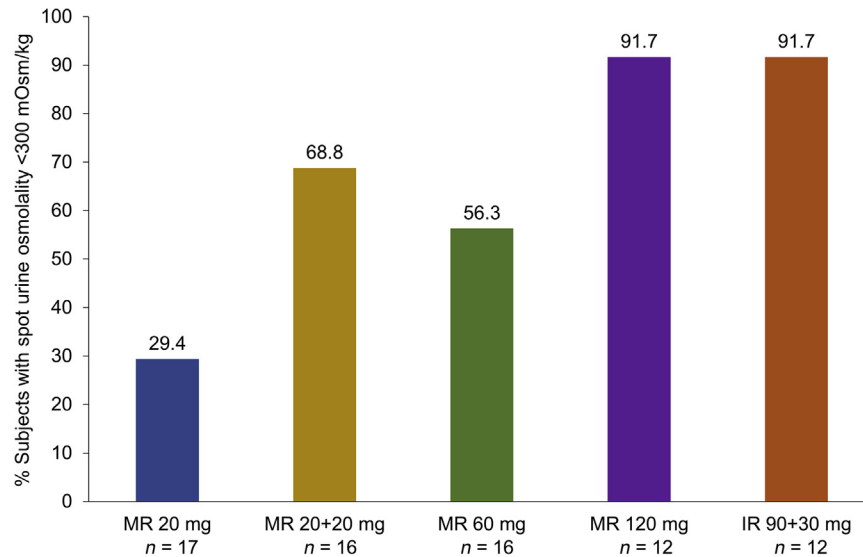
Table 3. Mean (SD) pharmacokinetic parameters on day 7 of tolvaptan treatment for 5 different dosage regimens in subjects with autosomal dominant polycystic kidney disease

	MR 20 mg ($n = 17$)	MR 20+20 mg ($n = 16$)	MR 60 mg ($n = 17$)	MR 120 mg ($n = 12$)	IR 90+30 mg ($n = 12$)
C_{max} (ng/ml)	140 (68.4)	175 (60.1)	350 (156)	669 (370)	716 (344)
t_{max} (h)[a]	6.00 (3.97–10.00)	6.00 (3.97–16.00)	6.00 (3.98–9.00)	5.98 (3.97–6.00)	2.00 (1.00–9.00)
AUC_{0-24h} (ng·h/ml)	1260 (654)[b]	2310 (704)	3600 (1670)[b]	7740 (3650)[b]	6570 (3230)
CL/F (ml/min/kg)	3.89 (1.70)	ND	4.37 (2.22)	4.11 (2.34)	ND
C_{min} (ng/ml)	14.7 (9.95)	50.8 (24.0)	51.1 (32.3)	139 (75.5)	57.5 (41.8)
C_{avg} (ng/ml)	52.6 (27.2)	96.3 (29.3)	150 (69.6)	322 (152)	274 (135)

AUC_{0-24h}, area under the concentration-time curve from time 0 to 24 hours postdose; C_{avg}, average plasma concentration during the dosing interval at steady state; C_{max}, maximum (peak) plasma concentration of the drug; C_{min}, minimum (trough) plasma concentration of the drug; CL/F, apparent total clearance of the drug from plasma following extravascular administration; IR, immediate release; MR, modified release; ND, not determined; t_{max}, time to maximum (peak) plasma concentration.
[a]Median (minimum–maximum). Figure 2 depicts median plasma tolvaptan concentrations over time, whereas the median t_{max} shown here was calculated from individual subject concentration-time curves. Hence the difference between the time of maximum tolvaptan concentration for IR 90+30 mg in Figure 2 (4 h) and the median t_{max} for IR 90+30 mg shown here (2 h).
[b]Values equal to AUC infinity, therefore CL/F determined.

Figure 3. Percentage of subjects with spot urine osmolality <300 mOsm/kg following 7 days of tolvaptan treatment for 5 different dosage regimens in subjects with autosomal dominant polycystic kidney disease. IR, immediate release; MR, modified release.

patient symptom burden due to urinary urgency increased by a mean of 1.4 points for MR 20 mg, 3.2 points for MR 20+20 mg, 3.2 points for MR 60 mg, 4.6 points for MR 120 mg, and 4.7 points for IR 90+30 mg. At the same time, reported impact due to urinary urgency increased by 0.9 points for MR 20 mg, 4.2 points for MR 20+20 mg, 3.5 points for MR 60 mg, 10.9 points for MR 120 mg, and 8.8 points for IR 90+30 mg.

At baseline, the patient-reported impact due to urinary frequency was a mean of 0.8 points on a 0- to 32-point scale, where higher scores indicate greater impact. During treatment, reported impact due to urinary frequency increased by a mean of 1.4 points for MR 20 mg, 4.6 points for MR 20+20 mg, 4.1 points for

MR 60 mg, 12.2 points for MR 120 mg, and 9.1 points for IR 90+30 mg.

Changes from baseline on the ADPKD Nocturia Quality-of-Life, ADPKD Urinary Urgency, and ADPKD Urinary Frequency Questionnaires for individual subjects were highly variable, and these changes were not correlated with changes in urine volume.

For subjects in group 1, tolvaptan MR 120 mg or IR 90+30 mg, the doses producing the largest daily urine volumes, were chosen as the least tolerable; only 2 subjects chose them as the most tolerable. For subjects in group 2, the tolvaptan MR 20 mg regimen, which produced the lowest increase in daily urine volume, was the most tolerable (10 of 13 subjects), and no
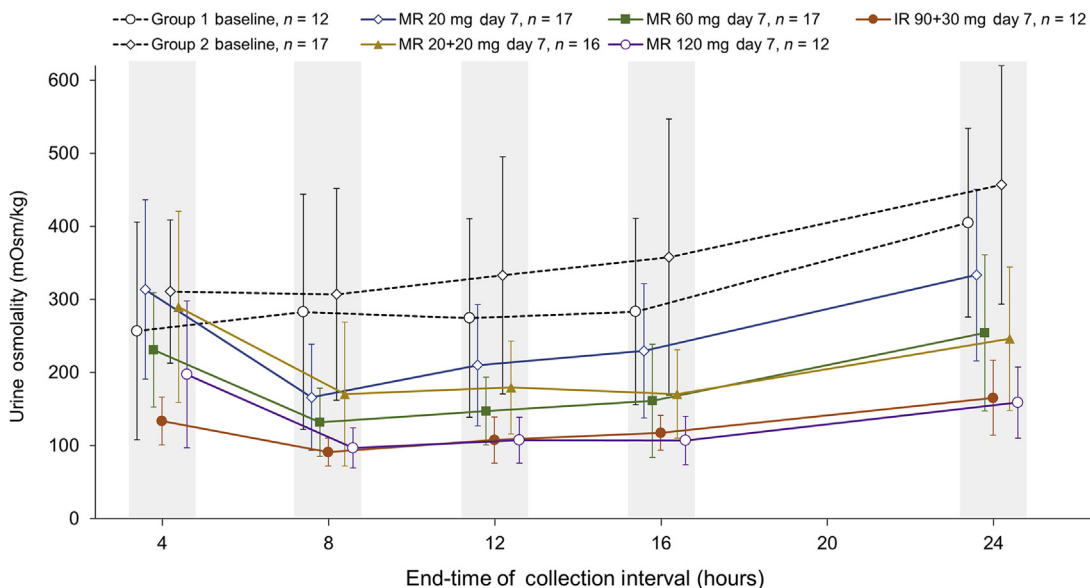
Figure 4. Mean (±SD) urine osmolality values at baseline (day 0) and on day 7 of tolvaptan treatment in subjects with autosomal dominant polycystic kidney disease. Data points are staggered for legibility. IR, immediate release; MR, modified release.

a

b
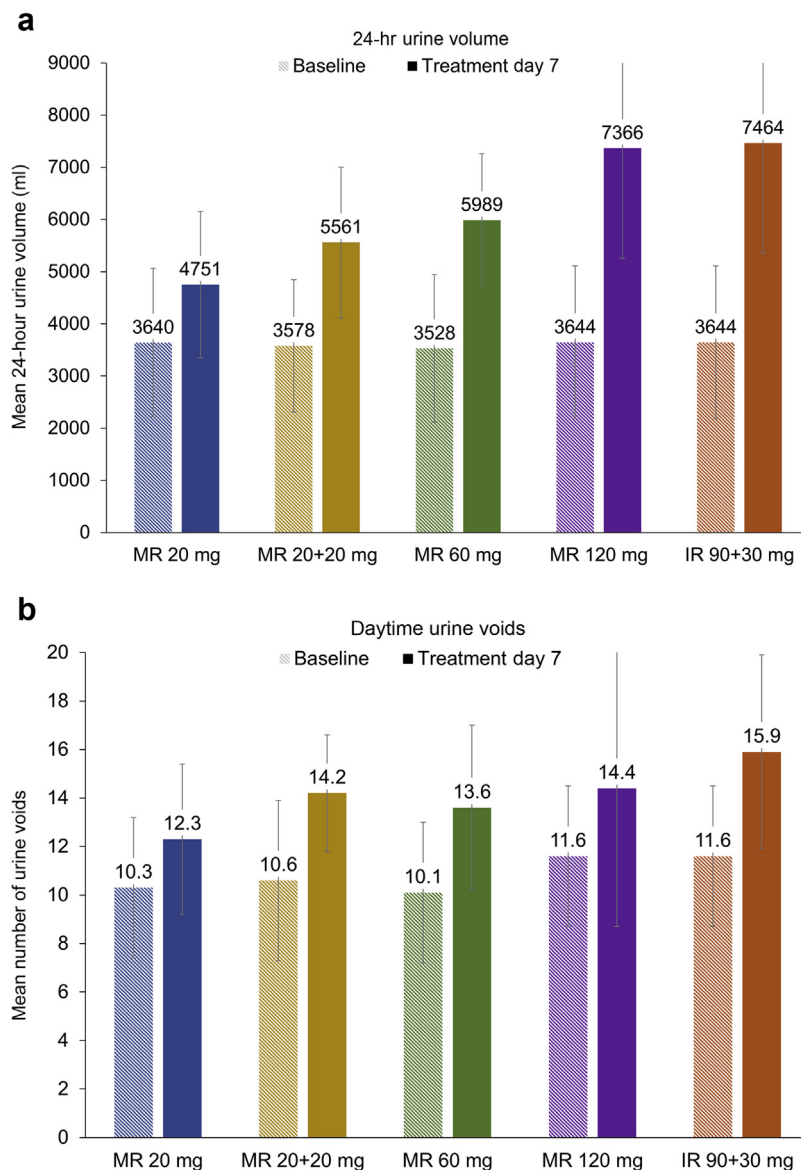
Figure 5. Mean (±SD) 24-hour urine volume (a) and number of daytime urine voids (b) at baseline and day 7 of tolvaptan treatment. As the initial treatment regimens in group 1, tolvaptan modified release (MR) 120 mg and immediate release (IR) 90+30 mg had the same baseline values.

subject chose MR 20 mg as the least tolerable. Group 2 subjects chose either MR 20+20 mg ($n = 7$) or MR 60 mg ($n = 6$) as least tolerable; 3 selected MR 60 mg as the most tolerable regimen.

Pharmacokinetic/Pharmacodynamic Correlations

The percentage of subjects with spot urine osmolality <300 mOsm/kg and average responses in urine osmolality $AUC_{0–24h}$ and 24-hour urine volume appeared to correlate with average tolvaptan exposure ($AUC_{0–24h}$) values, but at the individual level, responses were highly variable. For the ADPKD Nocturia Quality-of-Life, ADPKD Urinary Urgency, and ADPKD Urinary Frequency Questionnaires, mean changes correlated with mean tolvaptan exposure ($AUC_{0–24h}$) and C_{min}, with MR 20 mg having the lowest impact.

Responses for MR 20+20 mg were similar to MR 60 mg and those for MR 120 mg were similar to IR 90+30 mg; again, at the individual level, responses were highly variable.

Safety

TEAEs occurred more frequently and in similar percentages of subjects in the MR 20+20 mg (58.8%), MR 120 mg (66.7%), and IR 90+30 mg (58.3%) groups than in the MR 20 mg (29.4%) and the MR 60 mg (35.3%) groups (Table 4). No serious TEAEs or AEs leading to discontinuation from the study drug were reported in any dose group.

Among the most frequently reported TEAEs (i.e., those reported by at least 2 subjects in any dose group) were those expected due to the mechanism of action of tolvaptan: polyuria, thirst, micturition urgency,
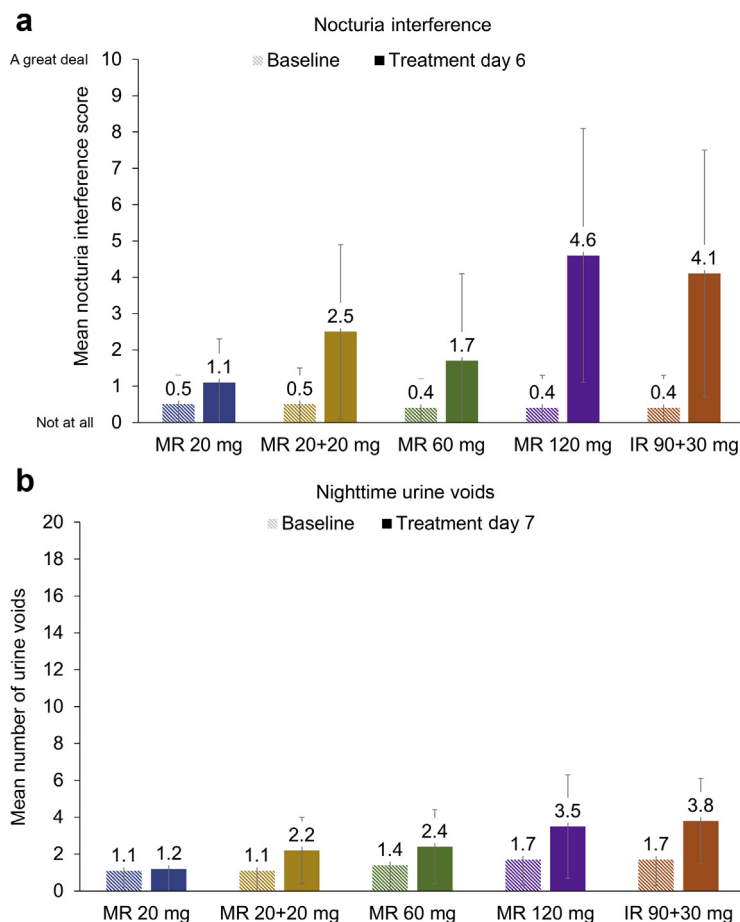
Figure 6. Mean (±SD) nocturia interference score from the Nocturia Quality-of-Life Questionnaire (range: 0 = not at all; 10 = a great deal) at baseline and day 6 of tolvaptan treatment (a) and number of nighttime urine voids at baseline and day 7 of tolvaptan treatment (b). As the initial treatment regimens in group 1, tolvaptan modified release (MR) 120 mg and immediate release (IR) 90+30 mg had the same baseline values.

nocturia, polydipsia, and pollakiuria. The only other TEAEs reported by at least 2 subjects in any dose group were nausea and headache. All TEAEs were mild or moderate in severity, except for 1 severe TEAE of vomiting reported in the MR 60 mg group. No laboratory test results that met criteria for drug-induced liver injury were reported (i.e., alanine aminotransferase or aspartate aminotransferase >3 times the upper limit of normal, either alone or in combination with other abnormal laboratory measurements).

DISCUSSION

This parallel-group, randomized, double-blind, placebo-controlled, multiple dose trial was conducted in subjects with ADPKD to compare the PK, PD, and tolerability of multiple doses of tolvaptan administered as either IR tablets or MR capsules.

Overall, the tolvaptan MR formulation exhibited predictable and dose-proportional PK, indicating the feasibility of using MR as a potential strategy to optimize its pharmacokinetic profile. Tolvaptan plasma concentrations at the end of the 24-hour dosing period were higher with tolvaptan MR 120 mg than with tolvaptan IR 90+30 mg. To explore the full PD range of tolvaptan responses, the doses/regimens selected for the current trial were chosen with the expectation that they would produce tolvaptan concentrations ranging from the minimally effective in increasing urine output to continually saturating and producing a maximal daily urine output. This expectation was confirmed: tolvaptan MR 20 mg produced minimal effects; tolvaptan MR 120 mg and IR 90+30 mg were equally saturating; tolvaptan MR 60 mg produced intermediate effects (falling between tolvaptan MR 20 mg and MR 120 mg). The tolvaptan MR 20+20 mg dose produced effects similar to those of the tolvaptan MR 60 mg dose.

Changes in urine osmolality and urine volume, along with scores on the ADPKD Nocturia Quality-of-Life, ADPKD Urinary Urgency, and ADPKD Urinary Frequency Questionnaires, appeared to correlate with average tolvaptan exposure (AUC_{0-24h}) and C_{min} values, but at the individual level, responses were highly variable. An increased patient-reported urinary burden

Table 4. Summary of adverse events by dose

n (%)	MR 20 mg (n = 17)	MR 20+20 mg (n = 16)	MR 60 mg (n = 17)	MR 120 mg (n = 12)	IR 90+30 mg (n = 12)
Subjects with AEs	5 (29.4)	10 (58.8)	6 (35.3)	8 (66.7)	7 (58.3)
AEs	17	27	11	23	18
Subjects with TEAEs	5 (29.4)	10 (58.8)	6 (35.3)	8 (66.7)	7 (58.3)
TEAEs	16	25	11	23	18
Subjects with serious TEAEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Subjects with severe TEAEs	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)	0 (0.0)
Subjects discontinued IMP due to AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Most frequent TEAEs[a]					
Polyuria	2 (11.8)	5 (29.4)	1 (5.9)	4 (33.3)	5 (41.7)
Thirst	1 (5.9)	3 (17.6)	2 (11.8)	2 (16.7)	1 (8.3)
Nocturia	1 (5.9)	2 (11.8)	1 (5.9)	1 (8.3)	3 (25.0)
Polydipsia	1 (5.9)	2 (11.8)	0 (0.0)	2 (16.7)	3 (25.0)
Pollakiuria	2 (11.8)	2 (11.8)	1 (5.9)	2 (16.7)	0 (0.0)
Micturition urgency	2 (11.8)	2 (11.8)	0 (0.0)	1 (8.3)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	1 (5.9)	2 (16.7)	1 (8.3)
Headache	0 (0.0)	2 (11.8)	1 (5.9)	1 (8.3)	0 (0.0)

AE, adverse event; IMP, investigational medicinal product; IR, immediate release; MR, modified release; TEAE, an AE that started after start of IMP treatment.
Individual TEAEs are Medical Dictionary for Regulatory Activities Preferred Terms.
[a]Most frequent TEAEs are listed in descending order by overall number of events across treatment groups.

and impact is expected with tolvaptan treatment, especially at higher doses, but the effect was less pronounced than expected with any of the dose groups. The increase of nocturia at higher doses, shown by the increased number of voids at night and associated with higher urine volume, did not translate into a noticeably higher burden based on subject reports, with moderate worsening reported for the MR 120 mg and IR 90+30 mg dose groups overall. The findings for urinary urgency and frequency were similar to those for nocturia. However, between the 2 highest dose groups, MR 120 mg and IR 90+30 mg, the immediate-release formulation had a numerically lower nocturia interference burden, potentially due to lower C_{min} values.

Tolvaptan IR 90+30 mg as a split dose and MR 120 mg QD were expected to show the greatest sensitivity if changes in the underlying PK profile improved tolerability. Within the context of the small number of subjects enrolled, the results of this study do not support the hypothesis that delayed absorption of tolvaptan following administration of the MR formulation and a time profile with only a single peak would improve the tolerability of tolvaptan. Nighttime concentrations do play a significant role in tolvaptan tolerability, however, as MR 60 mg and MR 20+20 mg, which had similar C_{min} values, had very similar tolerability profiles.

The incidences of AEs were as expected. Across the dose groups, the most frequently reported TEAEs were events related to the mechanism of action of tolvaptan. The frequency of reported urinary AEs was lower than the burden of urinary symptoms indicated by the ADPKD Nocturia Quality-of-Life Questionnaire, ADPKD Urinary Urgency Questionnaire, and ADPKD Urinary Frequency Questionnaire, possibly reflecting different elicitation methods, that is, patient reports about symptom burden on the questionnaires using targeted questions versus reporting of AEs through the investigator in response to broad questions about well-being.

Overall, the tolvaptan MR formulation exhibited predictable and dose-proportional PK in this study, indicating the feasibility of using MR as a potential strategy to simplify the dosing of tolvaptan. Regarding urinary symptoms, no improvement in tolerability was observed for the MR formulation relative to the IR formulation. The high interindividual variability in patient-reported tolerability, even among subjects experiencing similar effects on urine volume, suggests that the relationships of PK/PD to the patient experience of treatment are complex and subjective. Daily MR doses would need to be equivalent to the total daily dose of the IR formulation to produce the same physiological responses. Based on these findings, tolvaptan was further evaluated in the phase 2 NOCTURNE study (NCT01451827).[13]

DISCLOSURE

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