The NOCTURNE Randomized Trial Comparing 2 Tolvaptan Formulations

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Introduction: Tolvaptan, a treatment for autosomal dominant polycystic kidney disease (ADPKD), inhibits vasopressin V2 receptor signaling, which causes aquaretic adverse events (AAEs). The short-term efficacy and tolerability of a once-daily, modified-release (MR) formulation was assessed relative to the twice-daily, immediate-release (IR) formulation.

Methods: This Phase 2 multicenter, randomized (1:1:1:1), placebo-controlled, double-blind, placebo-masked, parallel-group study (NCT01451827) compared tolvaptan MR 50 mg once daily or tolvaptan MR 80 mg once daily with tolvaptan IR 60/30 mg daily split dose and placebo over 8 weeks in 177 subjects. The primary endpoint was percent change from baseline in total kidney volume (TKV) at week 3. Other endpoints included tolerability, assessed by adverse events and quality of life (QOL) measures.

Results: Mean percentage decreases in TKV at week 3 were observed for the pooled group of all (MR+IR) tolvaptan-treated subjects (−2.07%), tolvaptan MR 80 mg (−2.55%), and tolvaptan MR 50 mg (−2.46%) versus placebo (0.09%; $P < 0.02$ for each comparison with placebo), whereas the decrease with tolvaptan IR 60/30 mg (−1.17%; $P = 0.24$) did not reach significance. All tolvaptan regimens were associated with AAEs, but scores on ADPKD-specific and generic patient-reported outcome assessments showed little impact based on dosage on overall health-related QOL versus placebo.

Conclusion: Tolvaptan MR and tolvaptan IR demonstrated similar short-term efficacy, tolerability, and safety, with low impact on multiple measures of QOL. Conclusions regarding long-term efficacy are limited by the short duration of follow-up.

Alterations in the vasopressin–cyclic adenosine 3′,5′-monophosphate (cAMP) signaling pathway are central to ADPKD pathogenesis.[1,2] Tolvaptan inhibits kidney function decline in patients with rapidly progressing ADPKD via antagonism of the vasopressin V2 receptor. Twice daily dosing of tolvaptan targets constant (24-hour) suppression of V2 receptor signaling, where efficacy is measured using trough urine osmolality as a surrogate.[3] Phase 2 studies evaluated tolvaptan dosing regimens targeting urine osmolality <300 mOsm/kg (i.e., hypotonic compared to plasma osmolality).[4]

Inhibiting vasopressin's antidiuretic activity leads to AAEs, including increased urinary frequency, nocturia, and excessive thirst. An MR formulation of tolvaptan was developed to provide more gradual drug absorption than the IR formulation currently marketed and to achieve once-daily dosing. The MR formulation was evaluated under the hypothesis that lower and later peak and with similar overall plasma drug concentrations might provide constant inhibition of vasopressin V2 activity while minimizing AAEs associated with the IR formulation. Accordingly, we conducted a Phase

2 study (NCT01451827) to compare the efficacy, tolerability, safety, and pharmacodynamics of 2 doses of tolvaptan MR and 1 dose of tolvaptan IR in subjects with ADPKD.

METHODS

Study Design and Treatments

In this Phase 2, multicenter, randomized, placebo-controlled, double-blind, placebo-masked, parallel-group trial, subjects were randomized in a 1:1:1:1 ratio to tolvaptan MR 80 mg once daily (QD), tolvaptan MR 50 mg QD, tolvaptan IR 60/30 mg in a daily split dose, or placebo for 8 weeks (Figure 1).

Study treatments were administered in a split regimen using a combination of MR capsules (tolvaptan or placebo) and IR tablets (tolvaptan or placebo) to achieve full blinding (Figure 1). All subjects took the same number of tablets and capsules daily: subjects in the MR groups took a tolvaptan MR 50-mg or 80-mg capsule in the morning and tolvaptan IR placebo tablets in the morning and evening; subjects in the IR group took a tolvaptan MR placebo capsule in the morning and tolvaptan IR tablets in the morning and evening; and subjects in the placebo group took a tolvaptan MR placebo capsule in the morning and tolvaptan IR placebo tablets in the morning and in the evening. Subjects were instructed to take their morning dose upon awakening (nominally 8:00 AM) and their afternoon dose approximately 8 hours later.

The tolvaptan IR 60/30 mg split dose was selected for comparison to tolvaptan MR because it had become the most commonly used dose by subjects in ADPKD clinical trials at the time that the present trial was designed. The tolvaptan MR doses were selected based on results from a dose-finding trial of tolvaptan MR (NCT01210560), in which the area under the curve for tolvaptan MR 120 mg was approximately 18% higher

than for tolvaptan IR 90/30 mg.[5] Accordingly, tolvaptan MR 80 mg and 50 mg would be expected to pharmacokinetically approximate tolvaptan IR 60/30 mg and 45/15 mg. Subjects were instructed to drink to thirst during their participation in the trial to maintain blinding and to avoid dehydration.

Participants

Enrollment criteria included age 18 to 50 years and diagnosis of ADPKD by modified Ravine criteria, as follows: in subjects with a family history, at least 3 unilateral or bilateral kidney cysts for ages 18 to 39 years and at least 2 cysts per kidney for ages 40 to 50 years by sonography or 5 cysts per kidney if by computed tomography or magnetic resonance imaging; in subjects without a family history, 10 cysts per kidney by any radiologic method.[6] Additional inclusion criteria were eGFR >45 ml/min per 1.73 m^2 by the Chronic Kidney Disease Epidemiology Collaboration equation[7] and a minimum height-adjusted TKV by subject age to enrich the study population for rapidly progressing ADPKD. The minimum values were 230 to 308 ml/m for ages 18 to 24, 324 to 393 ml/m for ages 25 to 29, 413 to 641 ml/m for ages 30 to 39, 673 to 1044 ml/m for ages 40 to 49, and 1096 ml/m for age 50 years.

Exclusion criteria included use of diuretics within 14 days prior to randomization and a need for intermittent or constant diuretic use for any reason. Subjects with symptoms of frequent nocturia, as determined by medical history (>3 times waking at night) or urinary urgency were evaluated to exclude non-ADPKD genitourinary issues (e.g., incontinence, overactive bladder, or urinary retention). Other reasons for exclusion were liver disease, liver function abnormalities, serology other than that expected for ADPKD with cystic liver disease (i.e., normal except for possible alterations in alkaline phosphatase and
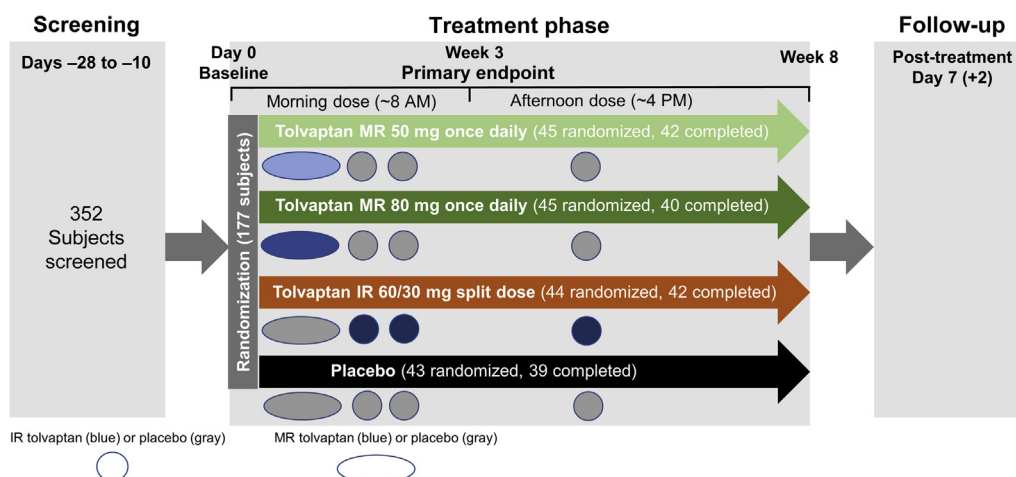

Figure 1. Study design. R, immediate release; MR, modified release.

Table 1. Questionnaires evaluating ADPKD-specific patient burden

Questionnaire	Domain/questions	Scoring
ADPKD-IS	Physical (7 questions) • Engage in leisure activities • Complete a full day's work at job or home • Conduct daily activities as usual regardless of pain • Complete everything in a day due to tiredness or exhaustion • Perform intense physical activities • Modify lifestyle due to pain or discomfort • Bothered by pain Emotional (4 questions) • Acceptance • Anxiety • Sadness • Feeling full before appetite satisfied Fatigue (3 questions) • Exhaustion or fatigue • Feeling tired while driving • Feeling fatigued after a good night's sleep	Each question is scored from 1 (not difficult at all/not bothered at all) to 5 (extremely difficult/extremely bothered) Each domain is scored separately, by summing the question scores in that domain and dividing by the number of questions completed[a]
ADPKD-UIS	Urinary Frequency (4 questions) • Daily activities • Social activities • Planning to use the bathroom • Urination frequency Urinary Urgency (4 questions) • Daily activities • Social activities • Planning to use the bathroom • Urination urgency Nocturia (3 questions) • Ability to sleep through the night • Waking up to urinate • Impact on everyday life	Each question is scored from 1 (not difficult at all/not bothered at all) to 5 (extremely difficult/extremely bothered) Each domain is scored separately, by summing the question scores in that domain and dividing by the number of questions completed

ADPKD, autosomal dominant polycystic kidney disease; ADPKD-IS, Autosomal Dominant Polycystic Kidney Disease Impact Scale; ADPKD-UIS, Autosomal Dominant Polycystic Kidney Disease Urinary Impact Scale.
[a]Four additional questions are not included in the domain scoring but can be used to provide additional insight into patient burden: guilt, sleep, size/shape of abdomen, urinary frequency/urgency.

γ-glutamyl transferase), and history of kidney surgery or cyst drainage within 6 months of randomization.

Outcome Measures

The primary endpoint was percent change in TKV from baseline at week 3. Prespecified secondary endpoints were percent change from baseline in TKV at week 8 as well as change from baseline to week 8 in total score on the Autosomal Dominant Polycystic Kidney Disease Urinary Impact Scale (ADPKD-UIS). To comply with ADPKD-UIS scoring instructions, the latter endpoint was replaced with reporting of individual ADPKD-UIS domain scores (Urinary Frequency, Urinary Urgency, and Nocturia domains).[8]

Furthermore, the trial assessed tolerability using disease-specific and generic patient-reported outcome (PRO) assessments, average number of urine voids during daytime and nighttime, as well as treatment compliance. Disease- and treatment-related quality of life were assessed using the domains of the Autosomal Dominant Polycystic Kidney Disease Impact Scale (ADPKD-IS), the ADPKD-UIS, the Short Form 12-item Health Survey (SF-12v2), and the Brief Pain Inventory Short Form (BPI-SF). Because the ADPKD-IS and ADPKD-UIS questionnaires were in the process of being qualified, their use in this trial was meant to support their applicability, sensitivity, and utility in assessment of ADPKD symptoms.

The ADPKD-IS (18 questions) measures ADPKD-related symptom burden over the past 2 weeks in 3 domains (Physical, Emotional, and Fatigue) (Table 1).[9] The ADPKD-UIS (11 questions) evaluates ADPKD-related daytime urinary burden (Urinary Frequency and Urinary Urgency domains) over the past week, as well as nighttime urinary burden (Nocturia domain).[8] On the ADPKD-IS and ADPKD-UIS, each domain is scored on a range of 1 to 5, with 1 indicating "not difficult at all" or "not bothered at all" and 5 indicating "extremely difficult" or "extremely bothered."

The SF-12v2 (7 questions) assesses generic health-related quality of life in the past month within 2 broad domains, the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores, each with a score range of 0 (worst) to 100 (best), with 50 as the expected value for the U.S. population based on the normative scoring algorithm.[10] The BPI-SF (9 questions) evaluates pain severity and the impact of pain on daily functioning and well-being (i.e., pain interference).[11] Pain severity (pain at its worst, at its least, on average over the past 24 hours, and currently) and pain interference over the past 24 hours (with

general activity, mood, walking ability, normal work, relationships, sleep, enjoyment of life) are evaluated on an 11-point numeric rating scale ranging from 0 (no pain/does not interfere) to 10 (as bad as you can imagine/completely interferes), in which higher scores indicate higher severity or impact.

Treatment compliance was measured as percentage of week 8 completers with >90% compliance by pill counts. Pharmacodynamic endpoints included percentages of subjects with spot urine osmolality <300 mOsm/kg at trough, 24-hour urine osmolality, and 24-hour urine volume.

Safety endpoints included adverse events (AEs) and clinical laboratory parameters. Given that tolvaptan is associated with risk for serious liver injury, an independent, blinded, expert committee adjudicated adverse events (AEs) of transaminase elevations by criteria developed for the assessment of tolvaptan clinical trial data.[12]

Assessment Schedule

Study participants made clinic visits during the screening period (28 to 10 days before baseline), at baseline/day 0 (randomization), week 3, and week 8. A follow-up telephone call for safety monitoring was performed 7 (+2) days after the last dose of study medication. Magnetic resonance imaging to assess kidney volume was performed during the screening period, at week 3, and at week 8. Subject questionnaires on symptom burden were administered at baseline and at week 8. The daily number of daytime voids and number of nighttime voids were self-reported using subject diaries for 5 days during screening, 5 days before the week 3 visit, and 5 days before the week 8 visit. The investigator assessed subjects for the occurrence of AEs at all trial visits. Clinical laboratory parameters (hematology, serum chemistry, urinalysis) were assessed at all clinic visits, and urine volume and osmolality were assessed at baseline, week 3, and week 8.

Statistical Analyses

In a previous study (NCT01336972), a change in TKV of −4.6% at week 3 during tolvaptan treatment (IR 90/30 mg) was observed; the measured SD was 5.4%. Assuming the same effect size and an SD of 5.4% for tolvaptan IR 60/30 mg or MR treatments at week 3 and a 0% effect size for the placebo group at week 3, a sample size of 40 subjects per treatment group would have 90% power to detect a significant difference at the 5% level. With a 1:1:1:1 randomization, the total sample size of the trial was 160; enrollment of 180 subjects was targeted to achieve 160 subjects with a readable magnetic resonance image at week 3.

Analyses of the primary and secondary efficacy variables were based on the intent-to-treat population observed cases dataset within the treatment period. Hierarchical testing was used to control the type I error in the primary analysis and conducted in the following order: (i) pooled tolvaptan treatment groups (IR and MR) versus placebo, (ii) tolvaptan MR 80 mg versus placebo, (iii) tolvaptan MR 50 mg versus placebo, and (iv) tolvaptan IR 60/30 mg versus placebo. If the primary hierarchical tests were all significant at 0.05, testing of the secondary efficacy variables using the same hierarchy and statistical tests would proceed. For the primary outcome, analysis of covariance was applied to log-transformed TKV with treatment as factor and baseline log-transformed TKV as covariate. Given that various tolvaptan IR and MR doses evaluated in a previous trial exhibited similar pharmacokinetic and pharmacodynamic profiles (NCT01210560), it was decided that the most informative statistical comparisons to make in the present investigation would be between the respective tolvaptan treatment arms and placebo.

Mixed-model repeated-measures analysis with factors of treatment, visit, and treatment visit interaction was conducted on the number of daytime and nighttime voids. Continuous pharmacodynamic variables were treated as change from baseline and analyzed by visit using analysis of covariance with treatment as factor and baseline as covariate. Chi-square (χ^2) testing was applied to the number of subjects with spot urine osmolality <300 mOsm/kg at trough 24-hour urine volume by visit. Safety data are reported as summary statistics.

Ethical Conduct

The study was conducted according to the International Conference on Harmonization Clinical Practice Consolidated Guideline and the applicable local laws and regulatory requirements of the sites at which the trial was performed. The study protocol and informed consent form were reviewed and approved by the governing institutional review board or independent ethics committee for each investigational site prior to trial start. Written informed consent was obtained from all subjects (or their guardian or legal representative).

RESULTS

Subject Characteristics and Disposition

Subject baseline demographics and clinical characteristics were well balanced among treatment groups (Table 2). Subjects had a mean eGFR of 85 ml/min per 1.73 m², indicating relatively preserved kidney function and suggestive of earlier disease compared to the Tolvaptan Efficacy and Safety in Management of

Table 2. Baseline demographics and clinical characteristics

| Variable | Tolvaptan | | | Placebo (n = 43) | Total (N = 177) |
	MR 50 mg (n = 45)	MR 80 mg (n = 45)	IR 60/30 mg (n = 44)		
Sex, n (%)					
Female	18 (40.0)	23 (51.1)	20 (45.5)	23 (53.5)	84 (47.5)
Male	27 (60.0)	22 (48.9)	24 (54.5)	20 (46.6)	93 (52.5)
Race, n (%)					
White	43 (95.6)	39 (86.7)	39 (88.6)	38 (88.4)	159 (89.8)
Black or African American	0 (0.0)	2 (4.4)	1 (2.3)	3 (7.0)	6 (3.4)
American Indian or Alaska Native	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Asian	1 (2.2)	3 (6.7)	2 (4.5)	0 (0.0)	6 (3.4)
Other	0 (0.0)	1 (2.2)	2 (4.5)	2 (4.7)	5 (2.8)
Ethnicity, n (%)					
Hispanic/Latino	2 (4.4)	4 (8.9)	5 (11.4)	4 (9.3)	15 (8.5)
Not Hispanic/Latino	43 (95.6)	40 (88.9)	39 (88.6)	39 (90.7)	161 (91.0)
Unknown	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.6)
Age, yr, mean (SD)	34.1 (10.0)	35.8 (7.9)	32.2 (7.6)	33.9 (8.1)	34.0 (8.5)
Height, cm, mean (SD)	176.9 (10.6)	173.1 (11.2)	175.7 (10.9)	173.0 (12.0)	174.7 (11.2)
Weight, kg, mean (SD)	81.5 (14.5)	79.4 (19.5)	80.8 (16.1)	82.8 (20.3)	81.1 (17.6)
TKV, ml, mean (SD)	1691.4 (940.9)	1797.4 (830.8)	1532.9 (760.1)	1728.8 (839.7)	1687.8 (844.3)
htTKV, ml/m, mean (SD)	948.9 (504.4)	1035.2 (457.3)	866.2 (405.8)	992.0 (457.2)	960.6 (458.2)
Estimated GFR, ml/min per 1.73 m^2, mean (SD)	86.9 (26.5)	83.0 (25.3)	86.4 (23.5)	85.1 (25.6)	85.4 (25.1)

GFR, glomerular filtration rate; htTKV, height-adjusted total kidney volume; IR, immediate release; MR, modified release; TKV, total kidney volume.

Autosomal Dominant Polycystic Kidney Disease and Its Outcomes (TEMPO) 3:4 population, which had a mean baseline eGFR of ∼81 ml/min per 1.73 m^2.[13] Subjects in this study also had a mean TKV (∼1.7 L) equivalent to that reported in the TEMPO 3:4 study, with a mean age of 34.0 years, which is approximately 5 years younger than the TEMPO 3:4 population, indicating a study population with more aggressive disease with more rapid TKV growth for a given age.

A total of 177 subjects were randomized, of whom 163 (92.1%) completed the study (Figure 1). Reasons for discontinuation were as follows: tolvaptan MR 50 mg: 2 adverse events, 1 protocol deviation; tolvaptan MR 80 mg: 3 lost to follow-up, 2 meeting withdrawal criteria; tolvaptan IR 60/30 mg: 1 adverse event, 1 withdrawal of consent; placebo: 2 lost to follow-up, 1 adverse event, 1 withdrawal of consent (Supplementary Figure S1). The study was conducted at 41 sites in the United States. Enrollment commenced in October 2011, and the last subject visit was in July 2013.

The frequency of subject-reported >90% medication compliance in each treatment group was as follows: MR 50 mg, 82.2%; MR 80 mg, 73.3%; IR 60/30 mg, 54.5%; and placebo, 69.8% (Figure 2).

Total Kidney Volume

In the primary efficacy analysis, the pooled tolvaptan treatment groups (MR+IR) (−2.07%, P = 0.0127), the tolvaptan MR 80 mg group (−2.55%, P = 0.0108), and the tolvaptan MR 50 mg group (−2.46%, P = 0.0155) each exhibited a significantly greater mean percent decrease in TKV from baseline to week 3 versus the placebo group (0.09%) (Figure 2). In the tolvaptan IR 60/30 mg group, TKV decreased significantly from baseline (−1.17%), but was not significantly different from placebo, potentially related to the lower level of medication compliance in this treatment group.

Given that the reduction of TKV by tolvaptan IR 60/30 mg at week 3 was not significant versus placebo, formal statistical testing could not be conducted on the week 8 data, according to the hierarchical testing procedure prespecified in the protocol. The reductions in TKV at week 8 from baseline were similar to those at week 3 (Figure 2). Differences in change from baseline versus placebo (P < 0.05) were seen for the pooled tolvaptan group, the tolvaptan MR 80 mg group, and the tolvaptan MR 50 mg group.

In addition to the primary efficacy analysis, which was based on observed cases data, a sensitivity analysis was conducted that incorporated all data, regardless of whether subjects were taking study drug. Mean percentage changes in TKV from baseline to week 3 in the sensitivity analysis were similar to those obtained in the primary analysis. Mean percentage changes in TKV from baseline to week 8 in the sensitivity analysis were: pooled tolvaptan, −1.61%; tolvaptan MR 80 mg, −2.48%; tolvaptan MR 50 mg, −1.43%; tolvaptan IR 60/30 mg, −0.96%; placebo, 0.96%.

Urinary Burden, Tolerability, and QOL

Baseline urinary burden for subjects in all treatment groups was similar, with subjects on average having a baseline 24-hour urine volume of 2.3 L with more than
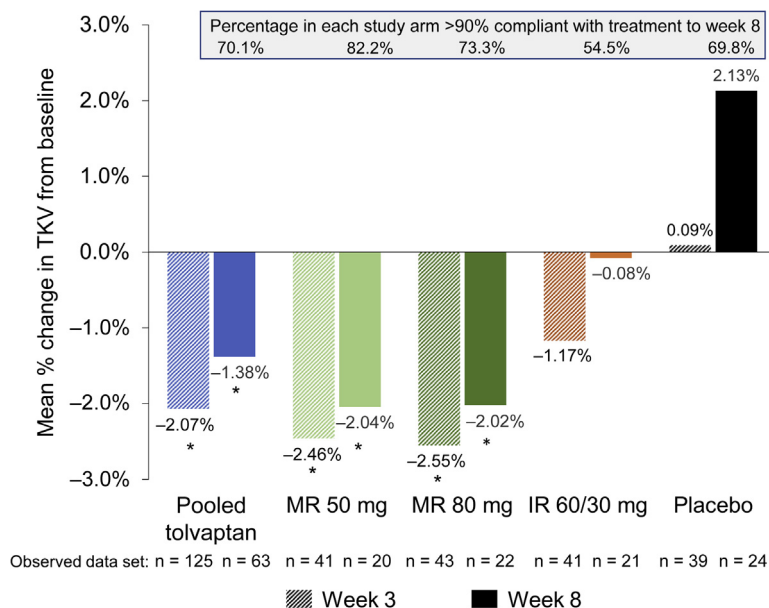
Figure 2. Percent change from baseline in total kidney volume at week 3 (primary endpoint) and week 8. Intent-to-treat population, observed cases. *$P < 0.05$. P values are for comparisons of tolvaptan week 3 versus placebo week 3 and tolvaptan week 8 versus placebo week 8. IR, immediate release; MR, modified release; TKV, total kidney volume.

6 daytime urine voids and 1.5 nighttime urine voids. At baseline, subjects on average reported being not bothered/not impacted by Urinary Frequency (mean, 1.2 points), Urinary Urgency (mean, 1.2 points), and Nocturia (mean, 1.5 points) as measured by the ADPKD-UIS.

During the trial, all tolvaptan groups experienced increased average daytime and nighttime urine voids compared to the placebo group ($P < 0.05$) (Figure 3). The average number of voids while subjects were awake was similar with tolvaptan MR 80 mg and tolvaptan IR 60/30 mg. Subjects in all tolvaptan groups had an increase in 24-hour urine volume at weeks 3 and 8 from baseline compared to the placebo group ($P < 0.0001$) (Figure 4).

All tolvaptan groups demonstrated an increased score from baseline to week 8 on the ADPKD-UIS Urinary Frequency, Urinary Urgency, and Nocturia domains compared to placebo subjects ($P < 0.001$), indicating increases in the burden of urinary symptoms from A Little Bothered/Impacted to Somewhat Bothered/Impacted (Figure 5) and driven by a shift to Very Bothered/Impacted and Extremely Bothered/Impacted in a small percentage of subjects (Supplementary Figure S2). The increased scores correlated with dose exposure, with the greatest increases for the tolvaptan IR 60/30 mg group (the group with the lowest compliance), followed by the tolvaptan MR 80 mg group, which were greater than for the tolvaptan MR 50 mg group. These findings are consistent with data from a dose-ranging study that found a dose-proportional pharmacodynamic profile for tolvaptan.[5] For the

placebo group, there was little change in all ADPKD-UIS domains, in line with the results for number of voids and 24-hour urine volume. ADPKD-IS domain scores were similar for tolvaptan and placebo at baseline (pooled tolvaptan/placebo scores for physical, 1.44/1.36; fatigue, 1.67/1.58; and emotional, 1.59/1.83) and week 8 (pooled tolvaptan/placebo scores for physical, 1.46/1.38; fatigue, 1.77/1.58; and emotional, 1.59/1.61).

SF-12v2 baseline scores in all groups were at or slightly above the established normative values for a normal US population (PCS and MCS scores of 50) and much above the established norm for a chronic kidney disease population (PCS = 38, MCS = 40), which aligns with findings for an untreated ADPKD population in chronic kidney disease stages 1–3.[9] Changes in score from baseline to week 8 on the PCS and MCS overall were small for all treatment groups (Supplementary Figure S3). Subjects in the tolvaptan IR 60/30 mg group had a numerical decrease on the PCS at -1.61 and the MCS at -2.24, driven by changes on the role physical, social function, role emotional, bodily pain, and vitality subscales, but still scored at or above the level of the normal U.S. population.

On the BPI-SF, all treatment groups showed no or very low levels of pain severity and pain impact at baseline, with minor changes in scores to week 8 on all BPI-SF subscales, which were not statistically significant for any tolvaptan group compared to the placebo group. The largest change was observed on the BPI-SF Worst Pain scale, which showed improvement from baseline to week 8 for pooled tolvaptan compared to placebo, treatment difference −0.61 (95% CI, −1.22
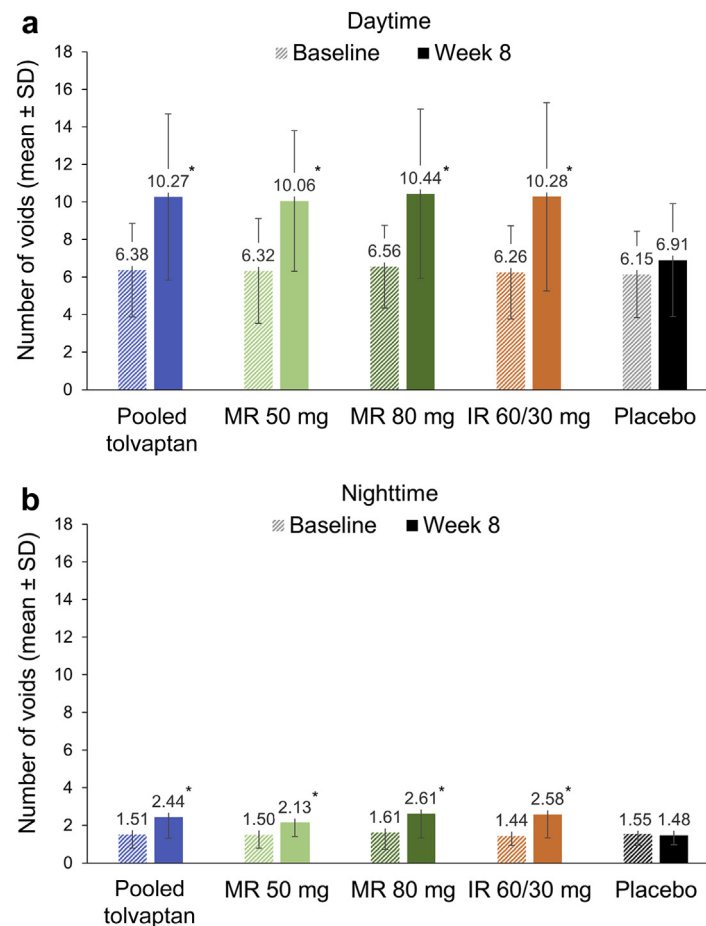
Figure 3. Number of (a) daytime and (b) nighttime urine voids. *$P < 0.05$ versus placebo. IR, immediate release; MR, modified release.

to −0.01) ($P = 0.0469$) in analysis of covariance with treatment group as factor and baseline as covariate (Supplementary Figure S4).

Pharmacodynamics

The number of subjects with spot urine osmolality <300 mOsm/kg at trough was greater for all tolvaptan groups compared to placebo ($P < 0.05$) at both week 3 and week 8 (Figure 6). Mean 24-hour urine osmolality (in mOsm/kg) ranged from 419.6 to 462.7 at baseline across treatment groups, with mean values at week 8 of 174.3 for pooled tolvaptan, 157.0 for IR 60/30 mg, 158.8 for MR 80 mg, 207.0 for MR 50 mg, and 408.4 for placebo. The change from baseline in 24-hour urine osmolality at
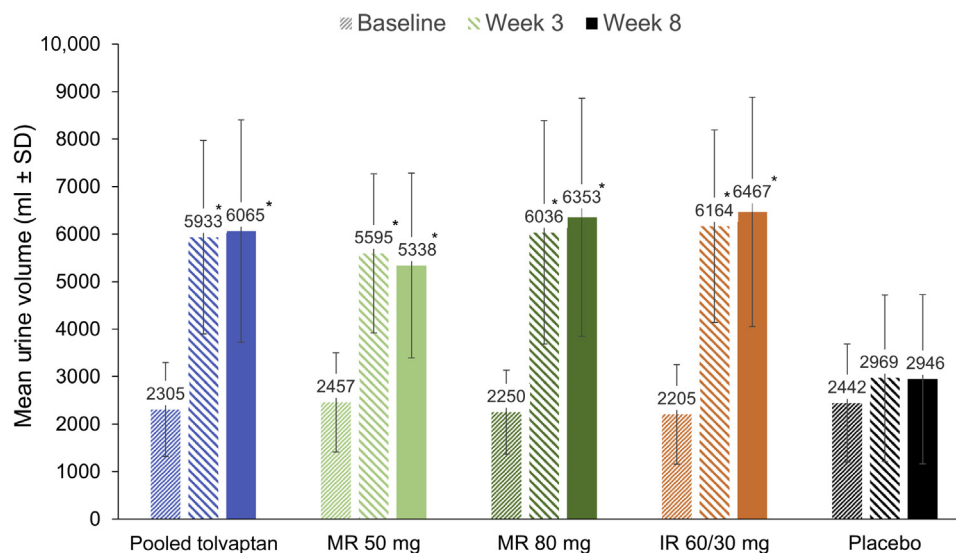

Figure 4. Twenty-four-hour urine volume. *$P < 0.0001$ versus placebo. IR, immediate release; MR, modified release.
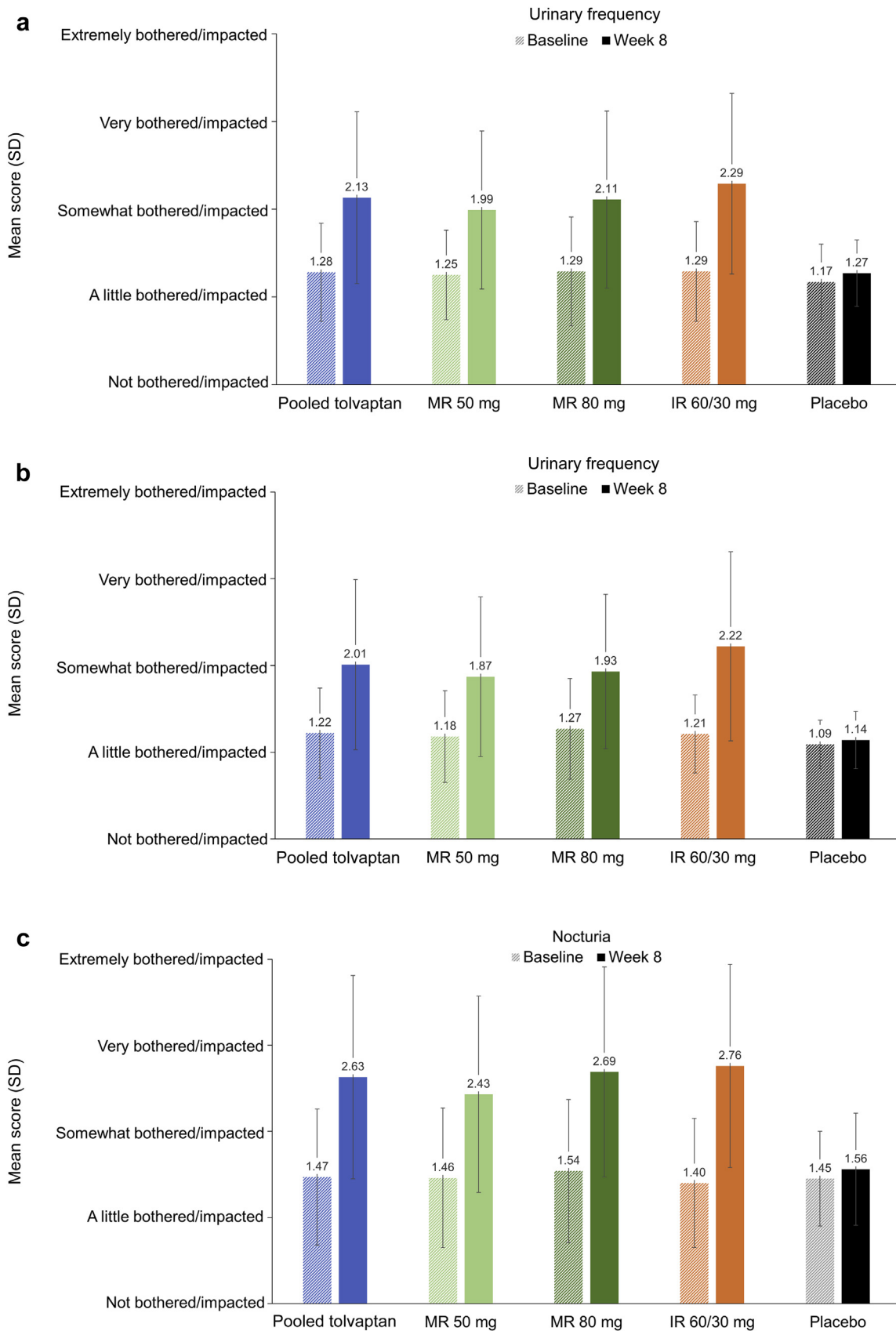
Figure 5. (a) Urinary Frequency, (b) Urinary Urgency, and (c) Nocturia domain scores on the Autosomal Dominant Polycystic Kidney Disease Urinary Impact Scale. Increases in score from baseline were significantly ($P < 0.001$) greater for each tolvaptan group versus placebo. IR, immediate release; MR, modified release.
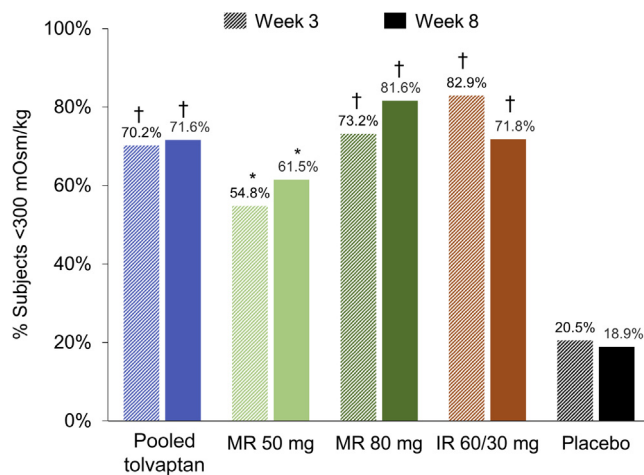
Figure 6. Subjects with spot urine osmolality <300 mOsm/kg at trough, week 3, and week 8. *P* values for comparison versus placebo. *$P < 0.01$; †$P < 0.0001$. IR, immediate release; MR, modified release.

week 8 was greater for each tolvaptan group compared to placebo ($P < 0.0001$) and correlated with the dose. The LS mean (SD) change from baseline in 24-hour urine osmolality (in mOsm/kg) was −275.5 (185.20) for pooled tolvaptan, −295.7 (195.55) for IR 60/30 mg, −284.3 (158.23) for MR 80 mg, −246.2 (200.26) for MR 50 mg, and −31.32 (144.72) for placebo.

Safety

The percentage of subjects who had at least 1 TEAE was highest for the tolvaptan IR 60/30 mg group and lowest for the placebo group (Table 3). As expected, AAEs such as thirst, polydipsia, nocturia, pollakiuria, and polyuria were reported at greater frequencies by subjects in the tolvaptan groups versus the placebo group. Frequencies of thirst, nocturia, polyuria, and pollakiuria were highest in the tolvaptan IR 60/30 mg group, followed in descending order by the tolvaptan MR 80 mg group, tolvaptan MR 50 mg group, and placebo group, reflecting a dose-dependent trend across the tolvaptan groups.

There were no deaths in the study. Serious TEAEs were reported for 6 subjects: dehydration and renal pain (in the same subject; tolvaptan MR 50 mg), sinus tachycardia (tolvaptan MR 50 mg), increased blood creatinine (tolvaptan MR 50 mg), increased alanine aminotransferase (ALT) (ALT 284 IU/L at week 3 visit; tolvaptan MR 80 mg), increased hepatic enzymes (ALT 123 IU/L and aspartate aminotransferase [AST] 59 IU/L at week 3 visit; placebo), and abnormal liver function tests (elevated ALT and AST levels before tolvaptan initiation, each increasing to >10 times the upper limit of normal during treatment, resulting in tolvaptan discontinuation; tolvaptan IR 60/30 mg). An additional, nonserious case of transaminase elevation met

adjudication criteria for hepatic TEAE: ALT 88 IU/L and AST 49 IU/L in a subject in the tolvaptan MR 50 mg group at day 20, leading to tolvaptan discontinuation. No concomitant increases in bilirubin suggestive of Hy's Law were observed in any of the 4 TEAEs meeting hepatic adjudication criteria, nor was any permanent liver toxicity reported.

DISCUSSION

The NOCTURNE study is the first randomized, controlled clinical trial with tolvaptan for the treatment of ADPKD to investigate QOL in multiple domains. We placed particular focus on evaluating urinary symptoms and their impact, given that patients report urinary problems as part of the burden of ADPKD,[14] and that tolvaptan increases urinary output by its mechanism of action. As expected, all tolvaptan treatment groups in this study experienced an increase in urine volume, an increase in daytime and nighttime voids, and a higher proportion of AAEs relative to placebo, differences that were reflected by increased Urinary Frequency, Urinary Urgency, and Nocturia scores on the ADPKD-UIS versus placebo ($P < 0.05$). The higher urinary burden experienced by subjects taking tolvaptan and the numerical increases in urinary burden in placebo subjects (all treatment groups were advised to increase fluid intake during the trial) were anticipated. However, mean ADPKD-UIS scores in tolvaptan subjects did not rise to a level indicating disruption of QOL, and scores on the ADPKD-IS and SF-12v2 showed minimal changes during the treatment period.

For the combined tolvaptan treatment groups, improvement relative to placebo ($P < 0.05$) was observed on the Worst Pain scale of the BPI-SF, a result consistent with reduction in ADPKD-related pain events seen in TEMPO 3:4.[13] Subjects in the placebo group had higher baseline scores for Worst Pain compared to the tolvaptan groups, which could indicate that subjects who were more susceptible to pain in the first place were randomized to the placebo group by chance. Other BPI-SF subscales showed little change to week 8 and no significant differences between tolvaptan and placebo groups. The lack of change observed on the BPI-SF overall is not surprising, given that subjects were already reporting very low levels of pain at baseline. In addition, information available from qualitative research into the use of the BPI-SF in ADPKD-related pain revealed that this instrument is not appropriate for assessment of pain in an ADPKD population, as ADPKD patients experiencing pain differentiate between dull chronic and severe acute types of pain with varying severity and impacts, whereas the BPI-SF uses a single construct of pain.[15]

Table 3. Summary of adverse events

Parameter	Tolvaptan MR 50 mg (n = 45)	Tolvaptan MR 80 mg (n = 44)	Tolvaptan IR 60/30 mg (n = 44)	Placebo (n = 42)	Total (N = 175)
Subjects with AEs	33 (73.3)	34 (77.3)	38 (86.4)	23 (54.8)	128 (73.1)
Subjects with TEAEs	30 (66.7)	33 (75.0)	38 (86.4)	22 (52.4)	123 (70.3)
Subjects with serious TEAEs	3 (6.7)	1 (2.3)	1 (2.3)	1 (2.4)	6 (3.4)
Subjects who discontinued study treatment due to AEs	5 (11.1)	0 (0.0)	2 (4.5)	1 (2.4)	8 (4.6)
Subjects who died	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Most commonly reported TEAEs (≥2% incidence overall)					
Gastrointestinal disorders					
Dry mouth	7 (15.6)	7 (15.9)	2 (4.5)	1 (2.4)	17 (9.7)
Nausea	2 (4.4)	1 (2.3)	2 (4.5)	4 (9.5)	9 (5.1)
Vomiting	1 (2.2)	1 (2.3)	2 (4.5)	2 (4.8)	6 (3.4)
Constipation	1 (2.2)	1 (2.3)	2 (4.5)	0 (0.0)	4 (2.3)
Diarrhea	0 (0.0)	1 (2.3)	1 (2.3)	2 (4.8)	4 (2.3)
General disorders and administration site conditions					
Thirst	15 (33.3)	15 (34.1)	19 (43.2)	6 (14.3)	55 (31.4)
Fatigue	3 (6.7)	2 (4.5)	6 (13.6)	1 (2.4)	12 (6.9)
Edema, peripheral	1 (2.2)	2 (4.5)	1 (2.3)	1 (2.4)	5 (2.9)
Infections and infestations					
Nasopharyngitis	3 (6.7)	1 (2.3)	0 (0.0)	1 (2.4)	5 (2.9)
Urinary tract infection	1 (2.2)	2 (4.5)	0 (0.0)	2 (4.8)	5 (2.9)
Metabolism and nutrition disorders					
Polydipsia	7 (15.6)	6 (13.6)	5 (11.4)	2 (4.8)	20 (11.4)
Decreased appetite	1 (2.2)	2 (4.5)	2 (4.5)	1 (2.4)	6 (3.4)
Nervous system disorders					
Headache	1 (2.2)	1 (2.3)	7 (15.9)	1 (2.4)	10 (5.7)
Dizziness	2 (4.4)	0 (0.0)	2 (4.5)	1 (2.4)	5 (2.9)
Renal and urinary disorders					
Nocturia	14 (31.1)	14 (31.8)	18 (40.9)	3 (7.1)	49 (28.0)
Polyuria	11 (24.4)	11 (25.0)	13 (29.5)	3 (7.1)	38 (21.7)
Pollakiuria	8 (17.8)	9 (20.5)	12 (27.3)	3 (7.1)	32 (18.3)
Renal pain	2 (4.4)	1 (2.3)	2 (4.5)	3 (7.1)	8 (4.6)
Micturition urgency	1 (2.2)	1 (2.3)	1 (2.3)	1 (2.4)	4 (2.3)
Vascular disorders					
Hypertension	2 (4.4)	2 (4.5)	3 (6.8)	2 (4.8)	9 (5.1)

AE, adverse event; IR, immediate release; MR, modified release; TEAE, treatment-emergent adverse event.
TEAE were defined as AEs that began after the start of treatment; or if the event was continuous from baseline and was serious, treatment-related, or resulted in death, discontinuation, interruption, or reduction of study treatment. All AEs were coded by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term.
All values are n (%).

A negative change from baseline in TKV at week 3 was seen in all tolvaptan groups and was significantly greater for the tolvaptan MR 80 mg and 50 mg groups, but not the tolvaptan IR 60/30 mg group, compared to the positive change for placebo. Results were comparable at week 8, although formal statistical testing was not possible, given that the hierarchical testing procedure was terminated when the IR 60/30 mg group failed at week 3 to reach significance versus placebo in the primary efficacy analysis. These data should be interpreted with caution. Within a context of anticipated reduction in TKV early during tolvaptan treatment due to its acute inhibition of cyst fluid secretion, measurements of small changes in TKV over very short periods of time (3 weeks or 2 months) suffer from imprecision.[16] An interval of at least 6 months is needed to reliably assess changes in TKV in patients with ADPKD.[17] Moreover, the percentage of subjects in

the IR 60/30 mg treatment arm with >90% compliance (54.5%) was lower than in the MR 50 mg (82.2%) and MR 80 mg (73.3%) study arms, which may have contributed to the absence of a statistically significant difference between IR 60/30 mg and placebo. Given that the IR 60/30 mg group did not have the highest frequency of discontinuations due to AEs (IR 60/30 mg, 2 of 44 [4.5%]; MR 50 mg, 4 of 45 [11.1%]; and MR 80 mg, 0 of 44), lower patient-reported compliance with IR 60/30 mg may have been related to the need for twice-daily dosing rather than any differences in tolerability.

With respect to pharmacodynamic activity, greater percentages of subjects in all tolvaptan arms achieved urine osmolality <300 mOsm/kg at trough compared to placebo. Mean changes from baseline in 24-hour urine osmolality and 24-hour urine volume were also greater in each tolvaptan treatment group versus placebo. Suppression of urine osmolality is a biomarker of

inhibition of vasopressin activity and correlates with reduction in the occurrence of clinical events related to ADPKD progression in patients treated with tolvaptan.[18] Data from a dose-ranging study indicate that the pharmacodynamic activity of tolvaptan and associated AAEs are proportional to tolvaptan dose, which is consistent with our findings.[5] The AAEs were manageable in our study, given that few subjects in any tolvaptan study arm discontinued treatment.

In summary, this trial demonstrates that tolvaptan IR twice daily and tolvaptan MR once daily both nominally suppress kidney growth in subjects with rapidly progressive ADPKD, with directionally similar efficacy and tolerability profiles. The small magnitude of the differences between tolvaptan MR and tolvaptan IR in this study indicates that a potentially large sample size and long duration of follow-up would be required in any future trial designed to more accurately discriminate differences in efficacy or tolerability between the formulations. Furthermore, for all tolvaptan doses and formulations evaluated, the impact of AAEs was moderate and not associated with substantial impairment in QOL. Strategies to manage the urinary burden of tolvaptan therapy, such as decreased dietary osmolar intake and adjustments to the timing of doses, enable patients to minimize urinary burden and to optimize tolvaptan tolerability.[19] Finally, the study adds to our knowledge of QOL in the ADPKD population. The assessment of outcomes important to patients and their caregivers has historically been underemphasized in ADPKD clinical trials,[20] and the inclusion of such patient-centric outcomes in future trials will enable patients and clinicians to make more informed decisions about the management of this condition.

DISCLOSURE

ACKNOWLEDGMENTS

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Subject disposition.

Figure S2. Scores on the Urinary Frequency, Urinary Urgency, and Nocturia domains of the Autosomal Dominant Polycystic Kidney Disease Urinary Impact Scale (ADPKD-UIS) at baseline and week 8.

Figure S3. Short Form 12-item Health Survey (SF-12v2) Physical Component and Mental Component Summary scores.

Figure S4. Brief Pain Inventory Short Form Worst Pain scale scores.

CONSORT Checklist.

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