Effects of the Soluble Guanylate Cyclase Stimulator Praliciguat in Diabetic Kidney Disease
A Randomized Placebo-Controlled Clinical Trial

John P. Hanrahan,1 Ian H. de Boer,1,2 George L. Bakris,1 Phebe J. Wilson,1 James D. Wakefield,1 Jelena P. Seferovic,1 Jennifer G. Chickering,1 Yueh-tyng Chien,1 Kenneth Carlson,1 Michael D. Cressman,1 Mark G. Currie,1 G. Todd Milne,1 and Albert T. Profy1

Abstract

Background and objectives Impaired nitric oxide signaling through soluble guanylate cyclase has been implicated in the pathophysiology of diabetic kidney disease. Praliciguat, a soluble guanylate cyclase stimulator that amplifies nitric oxide signaling, inhibited kidney inflammation and fibrosis in animal models.

Design, setting, participants, & measurements In a phase 2 trial, 156 adults with type 2 diabetes, eGFR 30–75 ml/min per 1.73 m², and urine albumin-creatinine ratio 200–5000 mg/g treated with renin-angiotensin system inhibitors were randomly allocated 1:1:1 to placebo, 20 mg praliciguat, or 40 mg praliciguat daily for 12 weeks. The primary efficacy and safety outcomes were change from baseline to weeks 8 and 12 in urine albumin-creatinine ratio and treatment-emergent adverse events, respectively. Other outcomes assessed were 24-hour ambulatory BP and metabolic parameters.

Results Of 156 participants randomized, 140 (90%) completed the study. The primary efficacy analysis demonstrated a mean change from baseline in urine albumin-creatinine ratio of −28% (90% confidence interval, −36 to −18) in the pooled praliciguat group and −15% (−28 to 0.4) in the placebo group (difference −15%; −31 to 4; P=0.17). Between-group decreases from baseline to week 12 for praliciguat versus placebo were seen in mean 24-hour systolic BP (−4 mm Hg; −8 to −1), hemoglobin A1c (−0.3%; −0.5 to −0.03), and serum cholesterol (−10 mg/dl; −19 to −1). The incidence of treatment-emergent adverse events was similar in the pooled praliciguat and placebo groups (42% and 44%, respectively). Serious adverse events, events leading to study drug discontinuation, and events potentially related to BP lowering were reported at higher frequency in the 40-mg group but were similar in 20-mg and placebo groups.

Conclusions Praliciguat treatment for 12 weeks did not significantly reduce albuminuria compared with placebo in the primary efficacy analysis. Nonetheless, the observed changes in urine albumin-creatinine ratio, BP, and metabolic variables may support further investigation of praliciguat in diabetic kidney disease.

Clinical Trial registry name and registration number: A Study to Evaluate the Soluble Guanylate Cyclase (sGC) Stimulator IW-1973 in Diabetic Nephropathy/Diabetic Kidney Disease as Measured by Albuminuria, NCT03217591

CJASN 16: 59–69, 2021. doi: https://doi.org/10.2215/CJN.08410520

Introduction

Diabetic kidney disease is a common and growing microvascular complication of diabetes, a major risk factor for cardiovascular events, and the leading cause of ESKD (1–6). The current standard of care for diabetic kidney disease includes glycemic and BP control together with pharmacologic blockade of the renin-angiotensin-aldosterone system (RAAS), but the prevalence of diabetic kidney disease has not changed despite increased use of these medications (3). Recently, new therapies, including sodium glucose cotransporter 2 inhibitors (7–10), glucagon-like peptide-1 receptor agonists (11,12), an endothelin receptor antagonist (13), and a mineralocorticoid receptor antagonist (14), have demonstrated promising kidney effects. Nonetheless, there remains clear need for additional therapies for diabetic kidney disease, including agents with new mechanisms of action.

Animal model data (15–18) and genetic evidence (19,20) indicate that reduced nitric oxide (NO) bioavailability leading to impaired 3’,5’-cyclic guanosine monophosphate (cGMP) signaling plays an important role in the pathogenesis of diabetic kidney disease. Phosphodiesterase 5 inhibitors, which inhibit breakdown of intracellular cGMP, have been shown to
reduce albuminuria in people with diabetic kidney disease (21,22). Soluble guanylate cyclase (sGC), a key enzyme in the NO-cGMP signaling pathway, catalyzes the formation of cGMP in response to NO binding. sGC stimulators, which sensitize sGC to NO and amplify cGMP production (23), could compensate for impaired NO signaling in diabetic kidney disease (24,25). Increasing NO-sGC-cGMP signaling in diabetic kidney disease could improve kidney blood flow and autoregulation (26), reduce glomerular permeability (27), inhibit kidney inflammation and fibrosis (28,29), and improve podocyte health (30). These effects could potentially prevent or slow the progression of diabetic kidney disease.

Praliciguat (IW-1973) is an orally available sGC stimulator characterized by extensive distribution to tissues, including the kidney medulla and cortex (23,31,32). Praliciguat inhibited proinflammatory and profibrotic responses in isolated human kidney proximal tubular cells (33) and ameliorated proteinuria and kidney damage in animal models of nephropathy, including at doses that had minimal effects on systemic BP in multiple rat models (34,35). In clinical studies of praliciguat in healthy adults and individuals with type 2 diabetes and hypertension (36,37), oral doses up to 40 mg were generally well tolerated and showed increases in plasma cGMP levels and modest decreases in systemic BP consistent with the expected vascular effects of NO signaling (23). Furthermore, in nonclinical studies (38) and in people with type 2 diabetes and hypertension (36), praliciguat showed promising effects on metabolic variables.

The goal of this study was to assess the tolerability and safety of praliciguat and evaluate its effects over 12 weeks on albuminuria, hemodynamic, and metabolic outcomes in participants with type 2 diabetes and diabetic kidney disease.

Materials and Methods
Study Design (NCT03217591)
This multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 2 clinical trial compared two dose levels of the sGC stimulator praliciguat (20 and 40 mg) versus placebo administered daily for 12 weeks (protocol is included in Supplemental Material). All participants gave written informed consent. The trial was conducted in accordance with the Declaration of Helsinki and ethical principles consistent with Good Clinical Practice.

Study Population
Eligible participants were age 25–75 years with type 2 diabetes and diabetic kidney disease, enrolled from 43 US sites. Participants were required to have an eGFR of 30–75 ml/min per 1.73 m² at screening and baseline by the Chronic Kidney Disease Epidemiology Collaboration equation. Participants were required to have albuminuria, as determined by spot urine albumin-creatinine ratio (UACR) >200 and <5000 mg/g at screening and baseline. In addition, participants had to be on stable doses of a RAAS antagonist (angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker) and at least one glucose-lowering agent for at least 28 days before random allocation to study treatment. Additional eligibility requirements are in Supplemental Material.

Intervention
Participants were stratified by baseline eGFR levels (30–45, >45–60, and >60–75 ml/min per 1.73 m²) and randomized 1:1:1 to 20 mg praliciguat, 40 mg praliciguat, or placebo using central randomization. The randomization schedule, prepared by an independent statistician, used a block size of three. The lowest randomization number within a stratum was assigned to the first participant who qualified for randomization, and subsequent assignments proceeded in increasing sequential order within a block. Participants and investigators were blinded to treatment assignments.

Praliciguat was provided as coated tablets in 10- and 20-mg strengths. Placebo tablets matched this appearance. During the first week, the total daily dose was taken in two doses (twice a day), and afterward, it was taken in 1 dose (once daily).

Primary Outcomes
The primary efficacy end point was change in UACR from baseline to weeks 8 and 12. Study visits were conducted at baseline (before randomization); at weeks 1, 4, 8, and 12; and 4 weeks after stopping treatment. First morning urine samples were collected on two consecutive mornings before each study visit; log-transformed UACR values were averaged for each visit. The primary efficacy analysis, change in UACR from baseline to weeks 8 and 12, was assessed using a repeated measures mixed effects model. The parameter estimates for each treatment group were estimated to provide 80% power to detect mean between-group difference in log UACR change of −0.376 units, corresponding to 31% between-group

Exploratory End Points
Exploratory end points included changes in eGFR, fasting glucose, hemoglobin A1c (HbA1c) (39), 24-hour hemodynamics measured by ambulatory BP monitoring, biomarkers, participant-reported outcomes (37), pharmacokinetic assessments, and safety laboratory assessments as detailed in Supplemental Material.

Statistical Analyses
The planned sample size of 150 participants (50 per treatment group) was estimated to provide 80% power to detect mean between-group difference in log UACR change of −0.376 units, corresponding to 31% between-group
reduction of geometric change from baseline in UACR, with a one-sided significance level of 0.05 (equivalent to two-sided significance level of 0.10). This assumed an SD of 0.67 units for between-group difference in log UACR change and dropout rate of 20%.

Efficacy analyses were performed on the intent-to-treat (ITT) population (all randomized participants who received one or more doses of study drug). The primary efficacy end point was analyzed using a mixed effects model repeated measures analysis with change from baseline in log-transformed UACR as the response variable; with treatment, visit, treatment by visit interaction, and baseline eGFR stratum as fixed effects; with baseline log UACR and baseline mean arterial pressure as covariates; and with subject as a random effect with "unstructured" as the variance-covariance structure. Least square means and associated 90% confidence intervals (90% CIs) were exponentiated and presented as geometric means. (Post hoc 95% CIs for least square means and mean differences for the ITT population are in Supplemental Table 1.) Exploratory change from baseline efficacy parameters used a similar repeated measures mixed effects model. Responder events were compared using a Cochran–Mantel–Haenszel test controlling for the stratification factor, baseline eGFR stratum. All hypothesis tests were presented as two-sided tests with a significance level of 10%, equivalent to a one-sided test with a 5% level. No multiplicity adjustments were performed because the focus was on estimation rather than inferential testing.

Causal mediation analysis was performed to estimate the effect on UACR attributed to direct effect of treatment, independent of BP response (Supplemental Material).

All safety parameters were evaluated descriptively for the safety population (all randomized participants who received at least one dose of study drug).

Results

Participant Characteristics

The study was conducted between August 1, 2017 and August 20, 2019 at 43 clinical trial sites in the United States. Among 503 subjects screened, 156 were eligible, randomized to treatment (Figure 1), and received at least one dose of study drug. Of the 140 participants (90%) who completed the study, 47 (94%), 42 (81%), and 51 (94%) were in the 20-mg praliciguat, 40-mg praliciguat, and placebo treatment groups, respectively. Reasons for early discontinuation are noted in Figure 1.

Demographic and clinical variables at baseline were well balanced across treatment groups (Table 1). Median age (interquartile range) in treatment groups was as follows: 65 (61–71) years for 20 mg praliciguat, 66 (60–69) years for 40 mg praliciguat, and 66 (58–70) years for placebo. Two-thirds of the participants were men, and the majority (87%) had baseline eGFR between 30 and 60 ml/min per 1.73 m². Median (interquartile range) UACR in each treatment group was as follows: 817 mg/g (344–1567) for 20 mg praliciguat, 882 mg/g (381–1536) for 40 mg praliciguat, and 881 mg/g (510–1615) for placebo. Most participants (71%) were White, 24% were Black, and the remainder were of other races. More than half (54%) reported Hispanic or Latino ethnicity.

Primary Efficacy Outcome

Decreases from baseline in UACR were evident after 1 week of treatment in each praliciguat dose group and appeared greater by week 12 (Figure 2). UACR did not decrease for the placebo group at weeks 1 and 4, but decreases were observed at weeks 8 and 12. The mean change (90% CI) in UACR from baseline over weeks 8 and
12 was $-28\%$ ($-36$ to $-18$) in the pooled praliciguat groups and $-15\%$ ($-28$ to $0.4$) in the placebo group (Table 2). The between-group range from baseline in UACR for the pooled praliciguat groups over weeks 8 and 12 (the primary efficacy end point) was $-15\%$ (90\% CI, $-31$ to 4; $P=0.17$; post hoc 95\% CI, $-33$ to 8) (Supplemental Table 1). UACR declines from baseline for each praliciguat treatment group were similar.

In the sensitivity analysis of change in UACR at week 12, UACR changed from baseline by $-35\%$ ($-48$ to $-19$) in the 20-mg praliciguat group, $-26\%$ ($-42$ to $-7$) in the 40-mg praliciguat group, and $-15\%$ ($-31$ to 6) in the placebo group. For the pooled praliciguat group, week 12 change from baseline was $-31\%$ ($-41$ to $-19$), a between-group difference of $-19\%$ ($-38$ to 6).

At the follow-up visit 4 weeks after completion of treatment, within-group geometric mean change in UACR from week 12 was 7\% ($5$ to $21$) for the pooled praliciguat group and 6\% ($9$ to $24$) in the placebo group.

A post hoc sensitivity analysis of the primary efficacy end point excluding all data from a single high-enrolling site was conducted after routine statistical data quality checks identified one site with data that were inconsistent with other sites. Findings supporting this post hoc analysis included negligible plasma praliciguat levels in most participants in the praliciguat treatment group at the site and a disproportionate number of participants with extreme ($\geq 75\%$) decreases from baseline in UACR. The site enrolled 23 participants (eight in the placebo group, nine in the 20-mg praliciguat group, and six in the 40-mg praliciguat group). Nine (39\%) of the 23 participants had decreases $\geq 75\%$ compared with four (3\%) of 133 participants in other sites. The post hoc efficacy analysis of the primary end point with participants from this site excluded showed a change from baseline in UACR for the pooled praliciguat group of $-24\%$ ($-31$ to $-15$), compared with $-4\%$ ($-17$ to 10) for placebo, with a change in UACR for the pooled praliciguat versus placebo of $-20\%$ ($-33$ to $-5$) (Supplemental Figure 1).

Exploratory analyses related to the proportion of UACR responders (Supplemental Figure 2) and change in eGFR (Supplemental Figure 3) are in Supplemental Material.
Blood Pressure and Heart Rate

All 24-hour ambulatory BP monitoring (ABPM) BP variables at week 12 showed declines from baseline in praliciguat versus placebo groups (Figure 3, Table 3). The pooled praliciguat group showed mean changes of −4 mm Hg in systolic BP and −3.0 mm Hg in diastolic BP versus placebo. The within-group mean BP declines from baseline were similar, with little difference between the 20- and 40-mg praliciguat groups. Small increases in 24-hour heart rate were observed in praliciguat-treated participants.

A mediation analysis indicated that 75% of the mean decline in UACR at week 12 was a direct effect and independent of the decrease in systolic BP assessed by 24-hour ABPM (Supplemental Figure 4). Mediation analyses on the basis of 12-hour daytime systolic BP assessed at weeks 4, 8, and 12 and 24-hour trough BP at week 12 were consistent with this result.

Metabolic Variables

Across treatment groups, there was little change from baseline in fasting plasma glucose over 12 weeks treatment (Table 3). HbA1c progressively decreased over 12 weeks in each praliciguat group compared with the placebo group (Figure 4). The between-group mean change from baseline to week 12 for the pooled praliciguat group was −0.3% (−0.5 to −0.03).

Decreases from baseline values at week 12 were observed for mean total (−10 mg/dl [−19 to −1]) and LDL serum cholesterol (−8 mg/dl [−15 to 0.1]) in the pooled praliciguat group compared with placebo; within-group reductions from baseline to week 12 for both cholesterol variables in the praliciguat groups were in the 3- to 8-mg/dl range. There were no meaningful changes from baseline to week 12 in serum triglycerides or weight, or in the homeostatic model assessment of insulin resistance in participants not on insulin (Table 3).

Table 2. Geometric mean change in urine albumin-creatinine ratio from baseline to weeks 8 and 12 (primary efficacy analysis)

<table>
<thead>
<tr>
<th>Evaluation Variable</th>
<th>Placebo, n=54</th>
<th>Praliciguat 20 mg, n=50</th>
<th>Praliciguat 40 mg, n=52</th>
<th>Praliciguat Pooled, n=102</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within group difference (90% CI)</td>
<td>−15% (−28 to −0.4)</td>
<td>−28% (−39 to −15)</td>
<td>−27% (−39 to −13)</td>
<td>−28% (−36 to −18)</td>
</tr>
<tr>
<td>Between-group difference (90% CI)</td>
<td>−16% (−33 to 6)</td>
<td>−15% (−33 to 8)</td>
<td>−15% (−31 to 4)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.21</td>
<td>0.27</td>
<td>0.17</td>
<td></td>
</tr>
</tbody>
</table>

P value refers to the between-group difference in change in urine albumin-creatinine ratio from baseline to weeks 8 and 12. Data were analyzed using a mixed effects model repeated measures analysis with change from baseline in log-transformed urine albumin-creatinine ratio as the response variable; treatment, visit, treatment by visit interaction, and baseline eGFR stratum as fixed effects; baseline log-transformed urine albumin-creatinine ratio and baseline mean arterial pressure as covariates; and unstructured as the variance-covariance structure. Geometric least square mean change (percentage) and the associated confidence intervals are derived as 100×[exp(least square mean change)−1]. 90% CI, 90% confidence interval. Differences are presented in bold.
Supplemental Material has exploratory efficacy analyses on biomarkers (Supplemental Table 2) and pharmacokinetics (Supplemental Figure 5).

**Tolerability and Safety**

A similar proportion of participants in all three treatment groups reported one or more TEAEs, although participants in the 40-mg praliciguat group reported a greater number of TEAEs compared with the 20-mg praliciguat and placebo groups (Table 4).

TEAEs judged to be related to treatment were reported in a greater proportion of participants in the 40-mg praliciguat group than in the placebo group, as were serious AEs. The 20-mg praliciguat and placebo groups had similar proportions of serious AEs. Nine participants (six in the 40-mg praliciguat group, two in the 20-mg praliciguat group, and one in the placebo group) prematurely discontinued study drug due to one or more TEAEs. Of these, two participants in the 40-mg praliciguat group discontinued due to syncope; both events were considered serious; Otherwise, there was no pattern suggested by events resulting in discontinuation (Table 4).

Among all study participants, gastrointestinal events were reported with greatest frequency (19 participants; 12%). Of these, only constipation and diarrhea were reported in >3% of participants, and only constipation occurred at a greater incidence in praliciguat-treated participants (four in praliciguat groups versus one in the placebo group).

TEAEs potentially related to BP lowering that were observed only in praliciguat-treated participants included dizziness (5; 5%) and syncope (2; 2%). All but one of the participants reporting dizziness and both participants reporting syncope were in the 40-mg praliciguat group.

Bleeding events were infrequently reported in praliciguat-treated participants (three participants), and none were serious AEs. An evaluation of platelet function by VerifyNow in a subset of 26 participants did not suggest platelet dysfunction or prolonged aggregation time for aspirin-like or adenosine diphosphate receptor assessments.

**Discussion**

This was the first randomized placebo-controlled trial to evaluate the safety and efficacy of an sGC stimulator in individuals with diabetic kidney disease. The trial did not meet statistical significance on its primary efficacy end point, the between-group change in UACR for the pooled praliciguat groups to weeks 8 and 12. However, point estimates of effect on albuminuria in the ITT population favored praliciguat, as did observed improvements in BP, HbA1c, and cholesterol.
In the pooled praliciguat group, mean UACR decreased from baseline by 28% at weeks 8 and 12. However, mean UACR in the placebo group also decreased (15%) at weeks 8 and 12, and the mean between-group change in UACR from baseline to weeks 8 and 12 in the pooled praliciguat group was −15 (−32 to 6). In a post hoc sensitivity analysis that excluded data from one site with a disproportionate number of participants with extreme decreases in UACR and negligible plasma praliciguat levels, the between-group change from baseline in UACR was −20% (−33 to −5). Reductions in UACR of this magnitude have been associated with improved clinical outcomes in observational (40) and longer-term clinical studies (41), but this study was not powered to assess effects of this size.

There are several mechanisms by which praliciguat treatment could reduce UACR. Mediation analyses performed on data from this study indicate that praliciguat’s effect on UACR was largely independent of systemic BP lowering. However, by amplifying NO-sGC-cGMP signaling in the kidney, praliciguat may decrease intraglomerular pressure, normalize glomerular permeability, ameliorate podocyte damage, improve tubular function, and/or reduce kidney inflammation and fibrosis (24,25), thereby reducing albuminuria. Effects on glomerular pressure, filtration barrier integrity, podocyte function, and cellular inflammation would be expected to occur quickly and could account for the reduction in UACR observed after only 1 week of praliciguat treatment. The increase in UACR observed 4 weeks after discontinuing study drug ("washout") and similarly reversible reductions in eGFR are also consistent with these mechanisms of action. In clinical trials of other drug classes, including RAAS antagonists (42,43) and sodium glucose cotransporter 2 inhibitors (7–10), acute declines in eGFR were followed by longer-term stabilization of kidney function. The full anti-inflammatory and antifibrotic effects of praliciguat may only be evident after longer treatment, and therefore, treatment effects beyond 12 weeks could be greater than those observed in this trial.

As in previous clinical studies (36,37), praliciguat treatment was associated with modest decreases in systemic BP and changes in heart rate, presumably compensatory. These hemodynamic effects are consistent with the known pharmacology of sGC stimulators (23). Uncontrolled hypertension is common in patients with diabetic kidney disease and is associated with higher kidney and cardiovascular risk (44). BP lowering could be beneficial in people with diabetic kidney disease and inadequately controlled BP.

In this study, praliciguat treatment was also associated with modest reductions in certain metabolic measures, including HbA1c and total and LDL cholesterol levels. This is consistent with clinical data on praliciguat in people with type 2 diabetes and hypertension (36), as well as findings from nonclinical studies (36,45,46). Possible mechanisms of the metabolic effects include improved insulin access to tissues, enhanced glucose uptake into skeletal muscle, improved insulin signaling, improved function of peroxisome proliferator–activated receptors, and improved mitochondrial function (47).

Evaluation of two praliciguat dose levels in this trial provided useful data to inform dose selection for future studies. Previous clinical studies found that up to 21 days of treatment with 40 mg praliciguat was adequately tolerated in healthy subjects (37) and individuals with type 2 diabetes and hypertension (37). The incidence of TEAEs was similar in the pooled praliciguat and placebo groups. Serious AEs, events leading to study drug discontinuation, and events potentially related to BP lowering were reported at higher frequency in the 40-mg praliciguat group and were similar in the 20-mg praliciguat and placebo groups.

Because effects on UACR, hemodynamic parameters, and HbA1c levels were similar for the 20- and 40-mg praliciguat groups, the 20-mg praliciguat dose may be most

| Table 3. Results for exploratory efficacy end points (change from baseline to week 12) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Variable        | Placebo         | Praliciguat     | Between-Group Difference |
|                 | (90% CI), n=54  | Pooled (90% CI), n=102 | (90% CI)         |
| UACR, %         | −15 (−32 to 6)  | −31 (−41 to −19) | −19 (−38 to 6)   | 0.20            |
| eGFR, ml/min per 1.73 m² | −1.4 (−3.1 to 0.4) | −2.8 (−4.1 to −1.3) | −1.4 (−3.6 to 0.7) | 0.27            |
| 24-h average systolic BP, mm Hg | −0.1 (−3 to 3) | −4 (−7 to −2) | −4 (−8 to −1) | 0.04            |
| 24-h average diastolic BP, mm Hg | 0.4 (−1 to 2) | −3 (−4 to −1) | −3 (−5 to −1) | 0.01            |
| 24-h average MAP, mm Hg | 0.3 (−2 to 2) | −3 (−5 to −2) | −4 (−6 to −2) | 0.01            |
| 24-h average heart rate, bpm | −2 (−4 to −1) | 1 (−0.1 to 2) | 3 (2 to 5) | 0.002           |
| Fasting plasma glucose, mg/dl | 3 (−10 to 16) | −4 (−14 to 6) | −7 (−23 to 9) | 0.47            |
| Hemoglobin A1c, % | −0.08 (−0.3) | −0.3 (−0.5 to −0.5) | −0.3 (−0.5 to −0.03) | 0.06            |
| HOMA-IR, subjects not on insulin | −0.8 (−4 to 3) | 0.8 (−2 to 4) | 2 (−3 to 6) | 0.53            |
| Cholesterol, mg/dl | 4 (−3 to 12) | −6 (−12 to 0.2) | −10 (−19 to −1) | 0.07            |
| LDL cholesterol, mg/dl | 3 (−4 to 9) | −5 (−10 to 0.3) | −8 (−15 to 0.1) | 0.10            |
| Triglycerides, mg/dl | −1 (−20 to 17) | 2 (−12 to 16) | 3 (−19 to 25) | 0.81            |
| Weight, kg | 0.5 (−1.0 to 2.0) | 0.7 (−0.4 to 1.9) | 0.2 (−1.5 to 2.0) | 0.83            |

Intention-to-treat population. For UACR, geometric least square means are used; for all other variables, least square mean changes and differences are used. 90% CI, 90% confidence interval; UACR, urine albumin-creatinine ratio; MAP, mean arterial pressure; HOMA-IR, homeostatic assessment of insulin resistance.

*Supplemental Table 1 shows post hoc 95% confidence intervals.

Table 1 shows n in each group.
suitable for evaluation in future trials in diabetic kidney disease.

Properties that differentiate praliciguat from other sGC stimulators (23) may make it attractive for investigation as a potential new therapy for diabetic kidney disease. Pharmacokinetic data from prior clinical trials showed that praliciguat has a high apparent volume of distribution, suggesting extensive distribution to extravascular tissues (36,37). Furthermore, in rodent studies, oral administration of praliciguat led to high tissue-plasma ratios in several

---

**Figure 4.** Changes in hemoglobin A1c in trial participants over 12 weeks. Least square mean change from baseline in hemoglobin A1c over 12 weeks.

---

**Table 4. Treatment-emergent adverse events**

<table>
<thead>
<tr>
<th>Adverse Event Type</th>
<th>Placebo, N=54, n (%) [events]</th>
<th>Praliciguat Dose Group, n (%) [events]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>20 mg, N=50</td>
</tr>
<tr>
<td>TEAEs</td>
<td>24 (44) [46]</td>
<td>21 (42) [42]</td>
</tr>
<tr>
<td>TEAEs related to study drug</td>
<td>6 (11) [8]</td>
<td>3 (6) [2]</td>
</tr>
<tr>
<td>TEAEs leading to discontinuation of study drug</td>
<td>1 (2) [1]</td>
<td>2 (4) [2]</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Body ache</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>2 (4)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Depression, worsening</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Eruption, increased</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Fluid overload</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Gastric acid reflux</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Papilledema</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Suicide attempt</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Syncope</td>
<td>2 (4)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Yeast infection</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

Verbatim event terms are presented. Percentages of participants with one or more adverse events are shown in parentheses. Numbers of adverse events are shown in brackets. N, number of participants studied; n, number of participants with one or more adverse events; TEAE, treatment-emergent adverse event.
organs, including the kidney (cortex and medulla), heart, liver, and adipose tissue (32). Kidney clearance of praliciguat is negligible in humans, suggesting it could potentially be used without dose adjustment in patients with reduced kidney function. Finally, the metabolic effects of praliciguat seen in this and other clinical studies (36) have not been reported in clinical studies of other sGC stimulators.

Strengths of this study include the randomized, placebo-controlled, prospective design; robust hemodynamic assessments by ABPM; and evaluation of two dose levels. Limitations include small sample size, short treatment duration, and data anomalies identified at one site. Furthermore, the study population was limited to participants with diabetic kidney disease and moderate to severe albuminuria; it is not known whether the results are generalizable to people with diabetic kidney disease and mild albuminuria or other kidney diseases.

In conclusion, in this phase 2 trial of people with type 2 diabetes and albuminuria on stable glucose-lowering and RAAS inhibitor therapy, the prespecified primary efficacy analysis did not show a statistically significant difference between praliciguat and placebo treatment in change in UACR. The AE profile was similar between the 20-mg praliciguat and placebo groups. Only longer-term clinical trials can determine the effect of praliciguat on clinical outcomes, such as slope of eGFR decline, doubling of serum creatinine, and/or onset of ESKD. On the basis of the changes observed in UACR, BP, and metabolic variables in this trial, further investigation of praliciguat as a potential therapy for diabetic kidney disease is warranted.

Disclosures

G.L. Bakris reports consultancy agreements with Alnylam, AstraZeneca, Bayer, Cyclerion Therapeutics, Ionis, Janssen, KBP, Merck, Novo Nordisk, Relypsy, and Vascular Dynamics; receiving research funding from Bayer, Novo Nordisk (funding for steering committee activities that goes to the University of Chicago), and Vascular Dynamics; receiving honoraria from AstraZeneca, Merck, Novo Nordisk, and Relypsy; serving as a scientific advisor or member of the American Heart Association, KBP, Merck, and Relypsy; and serving as Editor-in-Chief of American Journal of Nephrology, an Associate Editor for Diabetes Care, an Associate Editor for Hypertension Research, and Editor of UpToDate Nephrology.

K. Carlson reports employment by Wyss Institute at Harvard University and was a former employee of Cyclerion Therapeutics, Inc. J.G. Chickering reports employment by and ownership interest in Cyclerion Therapeutics, Inc. Y.-t. Chien was a former employee of and reports ownership interest in Cyclerion Therapeutics, Inc. M.D. Cressman was an employee of Covance Inc. at the time of the study and had stock in LabCorp, parent company of Covance Inc. M.G. Currie reports employment by and ownership interest in Cyclerion Therapeutics, Inc. I.H. de Boer reports consultancy agreements with Boehringer-Ingelheim, Cyclerion Therapeutics, Inc., George Clinical, Goldfinch Bio, and Ironwood Pharmaceuticals; receiving honoraria from the National Institutes of Health; serving as Deputy Editor of CJASN, as Associate Editor of Contemporary Clinical Trials, on the editorial advisory board of American Family Physician, and as Clinical Practice Guideline Cochair of Kidney Disease Improving Global Outcomes. I.H. de Boer has received equipment and supplies for research received by institution from Abbott and MedTronic. J.P. Hanrahan is currently a full-time physician employee of Dicerna Pharmaceuticals, a former employee of Cyclerion Therapeutics, Inc. and reports ownership interest in Cyclerion Therapeutics, Inc. G.T. Milne reports employment by and ownership interest in Cyclerion Therapeutics, Inc. A.T. Profy was a former employee of Cyclerion Therapeutics, Inc. and reports ownership interest in Cyclerion Therapeutics, Inc. and Ironwood Pharmaceuticals. J.P. Seferovic reports employment by and ownership interest in Cyclerion Therapeutics, Inc. J.D. Wakefield reports ownership interest in Cyclerion Therapeutics, Inc. P.J. Wilson reports employment by and ownership interest in Cyclerion Therapeutics, Inc.

Data Sharing Statement

Cyclerion Therapeutics, Inc. will share deidentified participant-level data that underlie the results of the primary analysis reported in this article with qualified researchers who are engaged in rigorous, independent scientific research. Datasets can be requested 18 months after the publication of this manuscript. Requests will be reviewed on a case-by-case basis. Access to data will be determined on the basis of the scientific merit of the research proposal and the exclusion of any potential conflict of interest or an actual or potential competitive risk. Additionally, requests must describe the measures that will be taken to secure the data. Upon approval of the request, execution of a data sharing agreement will be required. Anonymized individual participant-level data will be provided in a relational dataset (i.e., as an Statistical Analysis System or Comma Separated Variables file unless otherwise agreed upon); protocol and statistical analysis plan will also be provided with the dataset.

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN. 08410520/-/DCSupplemental.

Acknowledgments

The authors thank the participants in this study and acknowledge and thank Mr. Paul Miller (Cyclerion Therapeutics, Inc.) and the study teams (Cyclerion Therapeutics, Inc. and Covance Inc.) for their hard work conducting this study.

Because Dr. Ian H. de Boer is a Deputy Editor of CJASN, he was not involved in the peer review process for this manuscript. Another editor oversaw the peer review and decision-making process for this manuscript.

G.L. Bakris, K. Carlson, J.G. Chickering, Y-t. Chien, M.G. Currie, I.H. de Boer, J.P. Hanrahan, G.T. Milne, A.T. Profy, J.P. Seferovic, J.D. Wakefield, and P.J. Wilson were involved in trial design and/or analysis and interpretation of the data; J.P. Hanrahan and A.T. Profy drafted the manuscript; G.L. Bakris, K. Carlson, J.G. Chickering, Y-t. Chien, M.G. Currie, I.H. de Boer, G.T. Milne, J.P. Seferovic, J.D. Wakefield, and P.J. Wilson reviewed and revised it critically for important intellectual content; and all authors had access to the data and gave final approval of the submitted version.

Funding

This trial was funded by Cyclerion Therapeutics, Inc.

Disclosure

G.L. Bakris reports consultancy agreements with Alnylam, AstraZeneca, Bayer, Cyclerion Therapeutics, Ionis, Janssen, KBP, Merck, Novo Nordisk, Relypsy, and Vascular Dynamics; receiving research funding from Bayer, Novo Nordisk (funding for steering committee activities that goes to the University of Chicago), and Vascular Dynamics; receiving honoraria from AstraZeneca, Merck, Novo Nordisk, and Relypsy; serving as a scientific advisor or member of the American Heart Association, KBP, Merck, and Relypsy; and serving as Editor-in-Chief of American Journal of Nephrology, an Associate Editor for Diabetes Care, an Associate Editor for Hypertension Research, and Editor of UpToDate Nephrology.

K. Carlson reports employment by Wyss Institute at Harvard University and was a former employee of Cyclerion Therapeutics, Inc. J.G. Chickering reports employment by and ownership interest in Cyclerion Therapeutics, Inc. Y.-t. Chien was a former employee of and reports ownership interest in Cyclerion Therapeutics, Inc. M.D. Cressman was an employee of Covance Inc. at the time of the study and had stock in LabCorp, parent company of Covance Inc. M.G. Currie reports employment by and ownership interest in Cyclerion Therapeutics, Inc. I.H. de Boer reports consultancy agreements with Boehringer-Ingelheim, Cyclerion Therapeutics, Inc., George Clinical, Goldfinch Bio, and Ironwood Pharmaceuticals; receiving honoraria from the National Institutes of Health; serving as Deputy Editor of CJASN, as Associate Editor of Contemporary Clinical Trials, on the editorial advisory board of American Family Physician, and as Clinical Practice Guideline Cochair of Kidney Disease Improving Global Outcomes. I.H. de Boer has received equipment and supplies for research received by institution from Abbott and MedTronic. J.P. Hanrahan is currently a full-time physician employee of Dicerna Pharmaceuticals, a former employee of Cyclerion Therapeutics, Inc. and reports ownership interest in Cyclerion Therapeutics, Inc. G.T. Milne reports employment by and ownership interest in Cyclerion Therapeutics, Inc. A.T. Profy was a former employee of Cyclerion Therapeutics, Inc. and reports ownership interest in Cyclerion Therapeutics, Inc. and Ironwood Pharmaceuticals. J.P. Seferovic reports employment by and ownership interest in Cyclerion Therapeutics, Inc. J.D. Wakefield reports ownership interest in Cyclerion Therapeutics, Inc. P.J. Wilson reports employment by and ownership interest in Cyclerion Therapeutics, Inc.

Data Sharing Statement

Cyclerion Therapeutics, Inc. will share deidentified participant-level data that underlie the results of the primary analysis reported in this article with qualified researchers who are engaged in rigorous, independent scientific research. Datasets can be requested 18 months after the publication of this manuscript. Requests will be reviewed on a case-by-case basis. Access to data will be determined on the basis of the scientific merit of the research proposal and the exclusion of any potential conflict of interest or an actual or potential competitive risk. Additionally, requests must describe the measures that will be taken to secure the data. Upon approval of the request, execution of a data sharing agreement will be required. Anonymized individual participant-level data will be provided in a relational dataset (i.e., as an Statistical Analysis System or Comma Separated Variables file unless otherwise agreed upon); protocol and statistical analysis plan will also be provided with the dataset.

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN. 08410520/-/DCSupplemental.

Supplemental Material. Supplemental materials and methods and supplemental efficacy results.

Supplemental Table 1. Results from exploratory efficacy analyses: Change from baseline to week 12 and associated 95% confidence intervals.

Supplemental Table 2. Summary of biomarker results.

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN. 08410520/-/DCSupplemental.

Supplemental Material. Supplemental materials and methods and supplemental efficacy results.

Supplemental Table 1. Results from exploratory efficacy analyses: Change from baseline to week 12 and associated 95% confidence intervals.

Supplemental Table 2. Summary of biomarker results.
Trial of Praliciguat in DKD, Hanrahan et al.


Received: June 10, 2020 Accepted: October 30, 2020

Published online ahead of print. Publication date available at www.cjasn.org.