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Primary results of the randomized trial of metformin administration in polycystic kidney disease (TAME PKD).

Ronald D. Perrone MD[1], Kaleab Z. Abebe PhD[2], Terry Watnick MD[3], Andrew Althouse PhD[2], Kenneth R. Hallows MD PhD[4], Christina M Lalama MS, Dana C. Miskulin MD MS[1], Stephen L. Seliger MD MS[3], Cheng Tao MD[2], Peter C. Harris, PhD[5], Kyongtae Ty Bae MD, PhD, MBA[2]

1. Tufts Medical Center, Tufts University School of Medicine, Boston MA
2. University of Pittsburgh School of Medicine, Pittsburgh PA
3. University of Maryland School of Medicine, Baltimore MD
4. University of Southern California Keck School of Medicine, Los Angeles CA
5. Division of Nephrology and Hypertension, Mayo Clinic, Rochester, Minnesota

Corresponding Author:

Ronald D. Perrone MD

Division of Nephrology, Hospital Box 391

Tufts Medical Center

800 Washington Street

Boston, MA 02111

rperrone@tuftsmedicalcenter.org

Office: 617-636-0563; FAX 617-636-8329

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Abstract (247 words)

Autosomal dominant polycystic kidney disease (ADPKD) is characterized by growth of kidney cysts and glomerular filtration rate (GFR) decline. Metformin was found to impact cystogenesis in preclinical models of polycystic disease, is generally considered safe and may be a promising candidate for clinical investigation in ADPKD. In this phase 2 two-year trial, we randomly assigned 97 patients, 18-60 years of age, with ADPKD and estimated GFR over 50 ml/min/1.73 m^2, in a 1:1 ratio to receive metformin or placebo twice daily. Primary outcomes were medication safety and tolerability. Secondary outcomes included estimated GFR decline, and total kidney volume growth. Thirty-eight metformin and 39 placebo participants still received study product at 24-months. Twenty-one participants in the metformin arm reduced drug dose due to inability to tolerate, compared with 14 in the placebo arm (not significant). Proportions of participants experiencing serious adverse events was similar between the groups. The Gastrointestinal Symptoms Rating Scale score was low at baseline and did not significantly change over time. The annual change for estimated GFR was -1.71 with metformin and -3.07 ml/min/1.73m^2 per year with placebo (mean difference 1.37 {-0.70, 3.44} ml/min/1.73m^2), while mean annual percent change in height-adjusted total kidney volume was 3.87% in metformin and 2.16% per year in placebo, (mean difference 1.68% {-2.11, 5.62}). Thus, metformin in adults with ADPKD was found to be safe and tolerable while slightly reducing estimated GFR decline but not to a significant degree. Hence, evaluation of efficacy requires a larger trial, with sufficient power to detect differences in endpoints.

Key words: ADPKD, metformin, clinical trial, total kidney volume, eGFR

Introduction

Autosomal dominant polycystic kidney disease (ADPKD), the most common hereditary kidney disease, is characterized by the inexorable expansion of kidney volume driven by the growth of multiple cysts scattered throughout the kidney parenchyma.[1] Quality of life is impacted by cyst enlargement resulting in pain, cyst hemorrhage, cyst infection, hypertension, and nephrolithiasis. Liver cysts, which affect 80% of individuals with ADPKD, may also impact quality of life via cyst complications and hepatomegaly. Kidney failure by the middle of the sixth decade is the predictable outcome for more than half of affected individuals. Research progress has yielded substantial understanding of disease pathogenesis ranging from molecular genetics to downstream cell biological events; the existence of secondary events including interstitial inflammation and fibrosis; the impact of blood pressure control;[2, 3] and the contribution of these to disease progression. In addition to important lifestyle modifications (high water intake, reduced dietary sodium, weight control)[4] and control of hypertension,[2, 3] clinical trials to date have yielded one disease-modifying therapeutic agent, tolvaptan,[5, 6]with multiple phase 2 and 3 clinical trials in progress for other therapeutics. Despite the proven effect of tolvaptan to slow, but not stop, total kidney volume (TKV) growth and eGFR loss, limitations in tolerability from its aquaretic effects and potential liver injury indicate a need for additional therapeutic interventions.

Metformin has been used extensively for the treatment of diabetes and polycystic ovary syndrome for many years.[7]. Metabolic dysregulation in PKD is now a well-recognized phenomenon with increased aerobic glycolysis (the Warburg effect), impaired fatty acid oxidation, and reduced AMP-activated protein kinase (AMPK) activity.[8, 9] There is a strong rationale for the study of metformin in ADPKD due to its impact on cellular metabolism resulting in increased AMP-activated protein kinase (AMPK). Activation of AMPK in PKD could decrease cell proliferation via inhibition of the mTOR pathway[10] and decrease fluid secretion via inhibition of the cystic fibrosis transmembrane conductance regulator chloride channel,[11-14] processes essential to cyst formation and progression. Metformin may also inhibit cellular cAMP production, a key mediator of cyst growth, through inhibition of adenylyl cyclase.[15] In pre-clinical studies, metformin inhibited ADPKD kidney cyst growth and cell proliferation both *in vitro* and *in vivo* in both a rapid onset mouse and mini-pig model of

ADPKD.[16, 17] However, no beneficial effect of metformin was observed in a different, slowly progressive mouse ADPKD model, suggesting that the in vivo dosing regimen and/or the specific animal model used in pre-clinical studies are critical variables.[18]

The potential for lactic acidosis is a concern with use of metformin in study participants who are at risk for progressive loss of GFR. However, guidance from the FDA in 2016 (https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-revises-warnings-regarding-use-diabetes-medicine-metformin-certain) and position statements from Endocrine societies[19] have provided assurance that metformin could be used safely when eGFR is greater than 30 ml/min/1.73m^2. In addition to its salutary metabolic effects, which have been beneficial in preclinical ADPKD models, metformin is an attractive therapeutic agent because of its low cost. Additionally, there is extensive experience in long-term administration in humans. Because liver cysts exhibit the same pathophysiology as kidney cysts, there remains a possibility that metformin could have a favorable impact on hepatic cystogenesis.

Here we report the results of the Trial of Administration of Metformin in PKD (TAME PKD) study, which is a phase 2, parallel-group, randomized, double-blinded, placebo-controlled trial. The primary objectives were to investigate the tolerability, safety, and preliminary efficacy of metformin in adults with ADPKD.

METHODS

Trial Design and Oversight

Details of the clinical trial design have been described previously.[20] We enrolled 97 participants at Tufts Medical Center in Boston and University of Maryland in Baltimore from June, 2016 to December, 2018. Eligible persons were from 18 to 60 years of age, with a diagnosis of ADPKD as defined by unified Pei-Ravine criteria[21] and eGFR $\geq$ 50 ml/min/1.73m^2. There was no minimum total kidney volume requirement. Randomization was generated by the lead statistician at the data coordinating center, with participants assigned in a 1:1 ratio to receive metformin or matching placebo, stratified by clinical site. The schema was integrated into the web-based data management system, to which the clinical sites and investigational pharmacies had secure access. Consistent with the FDA-approved dosing guidelines for metformin, we selected a target dose of 1000 mg twice daily for use in this study. Metformin/placebo dosage was initiated at 500 mg daily and up-titrated at two-week intervals depending on eGFR, lactate levels, and tolerability. When eGFR was $\geq$30 ml/min/1.73m^2 and $\leq$45 ml/min/1.73m^2, maximum metformin/placebo dosage was 500 mg twice daily and eGFR was monitored monthly. Study medication was discontinued if eGFR was <30 ml/min/1.73m^2 but could be restarted if eGFR improved to $\geq$30 ml/min/1.73m^2.

Participants who reported that they could not tolerate the lowest dose were asked to continue in-person follow-up, questionnaires, and laboratory assessment including imaging. Telephone-based visits were permitted if participants were unable to come to the study center. Adherence to treatment was self-reported and confirmed by means of pill counts. The use of drugs interacting with metformin (nifedipine, furosemide, and cationic drugs such as amiloride, ranitidine, triamterene, digoxin, procainamide, quinidine, vancomycin, trimethoprim) was prohibited as was the use of tolvaptan.

The study conformed to the principles of the Declaration of Helsinki. The institutional review board at each site approved the protocol and written informed consent was obtained from all participants. A steering committee of investigators oversaw the trial design and conduct with the assistance of the independent data and safety monitoring committee and the designated Research Monitor. ClinicalTrials.gov Identifier NCT02656017.

Trial Assessments

Evaluations were performed at baseline, every two weeks through week 8 after randomization, monthly until 24 weeks from randomization, and then every 3 months through 24 months from randomization. Two months after completion of the 2 year follow-up period and termination of study drug, a final close-out visit was scheduled. Evaluations included physical examination; assessment of vital signs; assessments of quality of life, pain and tolerability; and blood and urine tests including urinary biomarkers. The serum creatinine level was measured in the clinical laboratory at each study site with the use of an IDMS (isotope dilution mass spectrometry) traceable method; eGFR was calculated using the CKD_{epi} equation.[22] For telephone visits, laboratory values were obtained at a commercial laboratory company; serum creatinine was measured using an IDMS-traceable method. Standardized MRI assessment of total kidney volume (TKV) and liver volume (LV) was performed at baseline, 6, 12, 18, and 24 months.[20] The full schedule of assessments is shown in Figure S1.

Mutation screening

Screening for likely pathogenic variants in patient peripheral blood derived DNA employed a next generation sequencing panel of 357 genes, including known PKD and ciliopathy genes plus candidates (Table S1). The panel captured the exonic and flanking intronic regions of each gene. The capture and sequencing protocol and scheme for detecting variants of interest were as described for a smaller panel.[23] Copy number variants were assessed by calculating the log2 ratio of actual read-depth over the expected read-depth for a given locus and confirmed by the multiplex ligation-dependent probe amplification assay.[24] In participants where no likely variants were identified, the sample was rescreened employing long range polymerase chain reaction (PCR) and Sanger sequencing of exons of the duplicated area of PKD1, as previously described,[25] but employing recently described long-range PCR primers.[24] All next-generation sequencing detected variants were also confirmed by targeted Sanger analysis. The pathogenic significance of variants was determined as outlined.[25 26 27]

Outcome Measures

The primary outcomes of the study are medication tolerability and safety. Medication tolerability was defined by: a) gastrointestinal symptom burden using the validated Gastrointestinal Symptoms Rating Scale (GSRS); b) response to the question “Can you tolerate this dose of the study drug for the rest of your life?”; and c) maximally tolerated dose at 24 months.[28, 29]

Safety was defined by adverse events and serious adverse events (SAE), including prospectively defined and ascertained hypoglycemia and lactic acidosis. The primary safety outcome was based on the proportion of participants experiencing at least one SAE during 24 months of study follow up. Vitamin B12 levels were monitored as levels may fall with metformin due to impaired absorption or bacterial overgrowth,[30]

Secondary outcomes include: a) ADPKD progression (height-adjusted TKV growth and eGFR decline); b) medication adherence; c) patient-reported pain and health-related quality of life; d) ESKD, death, and hospitalizations; and e) progression of hepatic cystic disease (height-adjusted LV). Changes in urinary biomarkers, including key metabolites and enzymes of the glycolytic pathway while on study drug, will be addressed in a separate publication.

Statistical Analysis

The statistical analysis plan has been previously published.[20] Sample size justification focused on ability to estimate 95% confidence interval (CI) widths for relevant point estimates within each study arm, similar to other pilot or phase II studies.[31] Assuming a 15% attrition rate through 24 months, a planned sample size of 96 afforded us the ability to estimate CI widths no larger than 21 for the primary tolerability outcome of GSRS summary score (or 0.81 for the mean score), 0.25 for the medication tolerability discontinuation outcome, and 0.16 for the safety outcome. All primary and secondary outcomes were described using sample means and sample proportions along with measures of sample variability. Volume outcomes from MRI were height-adjusted and natural log transformed in order to linearize with time. Participant demographics and baseline clinical characteristics were described between and within study arms, and variables with clinically meaningful associations and prognostic with outcome were included as covariates in the primary models. All primary outcomes were analyzed under intent-to-treat (ITT).

For the primary safety outcome, cumulative incidence between study arms and logistic regression was used to assess the association between study arms and the proportion of participants affected across serious adverse events. Linear mixed models were used to compare the change in the primary tolerability outcome (overall GSRS score) as a function of study time, the interaction between time and study arm, and clinical site. We included a random intercept to allow for participant-level variability of baseline GSRS. A significant interaction term indicated the change in tolerability over time differed between the metformin and placebo arms. To compare the cumulative incidence of not tolerating drug (assessed by the question “Can you tolerate this dose of the study drug for the rest of your life?”) between study arms, the Gray’s test of homogeneity for competing risks was used.

The annual rate of change in height-adjusted total kidney volume (htTKV) was compared between Metformin and Placebo arms using a Laird and Ware linear mixed model[32]. Natural log-transformed htTKV was modelled as a function of time, the interaction between time and study arm, and clinical site. In order to account for the participant-level variabilities of baseline log-transformed htTKV as well as rate of change, the model intercept and slope was allowed to vary. A significant interaction between time and study arm indicated a slowing of PKD progression due to metformin. This same model was used to evaluate total kidney cyst volume (TKCV), liver volume (LV), and liver cyst volume (LCV). For MRI measures, we estimated the annual percent change by deducing from theexponential of the annualized log-transformed slope minus 1 multiplied by 100. A similar model was used to compare eGFR between study arms.

Exploratory pain outcomes (back pain frequency, impact of pain on physical activity and sleep, and abdominal distension symptoms) were compared over time using similar linear mixed models as stated previously. Additional exploratory analyses were conducted to assess the effect of metformin on preliminary efficacy outcomes within risk groupings defined by Mayo Imaging Class[33] as well as genotype using linear mixed models. The Mayo Imaging Classification was used to divide participants into high (1C, 1D, and 1E) or low (1A, 1B, and 2) risk of progression.[33] Because of the small numbers of participants, it wasn’t possible to evaluate the impact of each independent genotype on htTKV or eGFR progression. Therefore, we grouped *PKD1* non-truncating, *PKD2*, and NMD mutations and compared the outcomes with *PKD1* truncating mutations. Additionally, we assessed the effect of metformin on the change in GSRS within subgroups defined by

baseline htLV and htLCV (>= upper tertile vs < upper tertile). These analyses were exploratory and hypothesis-generating in nature, rather than formal *a priori* subgroup analyses.

A sensitivity per-protocol analysis was performed on the safety, tolerability, and preliminary efficacy outcomes, restricting to participants who successfully completed drug titration with a maximally tolerated dose. Due to the COVID-19 global pandemic, additional sensitivity analysis was conducted for GSRS, htTKV, and eGFR using actual visit, MRI, or sample collection dates as opposed to the study visit designation (e.g., F6) to assess whether protocol deviations due to COVID-19 (e.g., missed or late visits) impacted the primary results.

Adherence (defined as $\geq$80% of proportion of pills taken) was compared between study arms using Chi-squared tests of independence. All pre-specified primary analyses (tolerability, safety, and preliminary efficacy) were compared between study arms with a 5% threshold of type I error; for exploratory analyses, point estimates and effect sizes were calculated along with 95% CIs. While several outcomes had data collected at 26 months after randomization (post-intervention visit), all primary and secondary analyses were conducted using the first 24 months of data, which coincided with the intervention. SAS 9.4 was used for all statistical analyses.

RESULTS

Patients

Of 108 participants assessed for eligibility, 97 were randomized with 49 participants assigned to metformin and 48 to placebo (Fig. 1). Overall, 9 (18.4%) of the metformin participants and 6 (12.5%) of the placebo participants withdrew from the study for reasons including but not limited to study burden, discontinuation of study medication, or adverse events. Only 2 participants (1 from each study arm) withdrew to begin Tolvaptan treatment, and no participants were lost to follow-up. Thirty eight participants (77.6%) assigned to metformin and 39 (81.3%) assigned to placebo were still receiving study product at the end of 24-month follow up (Fig. 1). Mean follow-up was 23.3 (7.2) months with little difference between the metformin-treated participants (22.1 (8.5) months) and the placebo participants (24.4 (5.5) months). Across the two groups, visit completion rates (the proportion of participants completing expected visits) ranged from 95 to 100%. Approximately 89% in the metformin and 81% in the placebo group met the adherence threshold of $\geq$80%. Fewer in-person visits were conducted during the initial COVID-19 pandemic surge, particularly from March to August, 2020. Twenty-three visits occurred after March 1, 2020, 12 of which were missing either htTKV or eGFR, but all had GSRS. These visits comprised 14 participants (5 Metformin, 9 Placebo). The last study visit was completed in December 2020. Demographic and clinical characteristics at baseline were balanced between the two study groups (Tables 1, and S2). Baseline eGFR (ml/min/1.73 m^2) was comparable: 86 (20) for metformin and 86 (19) for placebo. The distribution of genotypes was similar although *PKD1* mutations were somewhat more common in the metformin group, 78% vs. 61%. Among *PKD1* mutations, the proportion of those truncating were equally distributed between the groups (65% metformin; 64% placebo). This distribution was reflected in the Mayo Imaging Class (1C, 1D, and 1E) in the metformin group (50%) vs. 46% in the placebo group.

Primary Outcomes

The burden of gastrointestinal symptoms as measured by the Gastrointestinal Symptom Rating Scale was similarly low at baseline between treatment groups (metformin = 1.4 {1.3, 1.5} vs placebo = 1.3 {1.2, 1.5}) and did not significantly change over time (annual change = -0.02 {-0.09, 0.05} vs -0.06 {-0.12, 0.02}; P=0.50) (Fig. 2). There were slightly higher GSRS values for abdominal pain, indigestion, and diarrhea in the metformin group during the initial dose titration period, however, no differences persisted between arms. The distribution

of the highest achieved dosages of study medication was no different between study arms with 67% of metformin participants and 81% of placebo participants taking 2000 mg (P=0.21). Twenty-one participants (43%) in the metformin arm reduced drug dose due to inability to tolerate ("Can you tolerate this dose of the study drug for the rest of your life?"), compared with 14 (29%) in the placebo arm (P=0.12). Among the 21 participants who reduced metformin due to intolerance, the distribution of dosage at the time of reduction was 10, 5, 33, and 52% for 500, 100, 1500, and 2000 mg, respectively. Among the metformin participants that were followed through 24 months, 44% were on the highest dose **(**Table S3)**.** Study medication was discontinued completely for any reason by 22% (11) in the metformin arm and 19% (9) in the placebo arm (P = 0.80).

Adverse Events

The proportion of participants experiencing at least one serious adverse event (Table 2) was similar between the two treatment groups (8.2 vs 8.3%; P=0.98). There was one death in the metformin group due to suicide and no events of kidney failure requiring kidney replacement therapy. The death was not thought by the investigators (who were unaware of the study assignments) to be related to study medication or study participation.

Secondary Outcomes

The mean annual percent change in htTKV was 3.87 and 2.16% per year in the metformin and placebo groups, respectively (mean difference 1.68 {-2.11, 5.62}; P=0.38) (Table 3, Fig. 3). The annual decline for eGFR was -1.71 in metformin and -3.07 ml/min/1.73m^2 per year in placebo (mean difference 1.37 {-0.70, 3.44} ml/min/1.73m^2; P=0.20) (Fig. 4). Comparison of kidney cyst, liver, and liver cyst volumes at study visits and growth rates revealed no difference between the two treatment groups (Table 4, Table S4), while the mean annual percent changes in the volume measurements within the groups were all positive. General measures of well-being as expressed by the SF 36 mental component and physical component scores were similar to the general population, did not change over time, and were not significantly impacted by study medication (Table 5).

Exploratory Analyses

The frequency of back pain or abdominal fullness interfering with ability to perform usual physical activities was low and the rate over time did not differ between treatment groups (Table 6). The potential interference of pain with sleep or strenuous physical activity also did not differ between treatment groups with respect to the rate over time (Table 7). Blood pressure was well controlled throughout the trial and did not differ between treatment groups (Fig. , S2).

The effect of metformin on the annual rate of increase in htTKV was 0.07% per year ({-3.17, 3.42}; P=0.97) in the high-risk imaging group vs. 2.43% per year in the low-risk imaging group ({-4.13, 9.45}; P=0.47) (Table S5). The effect of metformin on eGFR decline in the high-risk group was (difference in annual rates of change between metformin and placebo) 1.32 ml/min/1.73m^2 {-1.63, 4.26}; P=0.38) and was 1.10 ml/min/1.73m^2 over 2 years {-1.85, 4.03}; P=0.47) in the low risk group (metformin minus placebo). Similar patterns emerged when the effect of metformin was assessed within genotype risk groups. The effect of metformin on the annual rate of increase in htTKV was minimal in the high-risk *PKD1* truncating mutation group (metformin minus placebo difference of -0.38% per year {-4.30, 3.70}; P=0.85) vs. 2.77% per year (metformin minus placebo) ({-3.60, 9.57}; P=0.39) in the low-risk group. The effect of metformin on annual eGFR decline was 1.47 ml/min/1.73m^2 ({-1.89, 4.82}; P=0.39) high-risk group and 1.54 ml/min/1.73m^2 ({-1.24, 4.32}; P=0.28) in the low-risk group. Exploratory subgroup associations for GSRS, htLV, and htLCV are shown in Table S5.

The mean difference in annual eGFR decline among study completers was 1.24 ml/min/1.73m^2 (-0.91, 3.38; P=0.26) favoring the metformin group (1.89 ml/min/1.73m^2 {-3.39, -0.32} vs. 3.09 ml/min/1.73m^2 {-4.59, -1.60}).

Results of the per-protocol analyses were similar to the primary analyses for tolerability, safety, and preliminary efficacy outcomes among the 49 participants (51%) who successfully completed drug titration with a maximally tolerated dose. GSRS did not significantly change over time (annual change = -0.09 {-0.18, 0.001} vs -0.03 {-0.11, 0.05}; P=0.32). The proportion of participants reducing drug dose due to inability to tolerate was not significant (41 vs 22%; P=0.12). The proportion of participants experiencing at least one serious adverse event was similar between the two treatment groups (9.1 vs 0%; P=0.20). The mean annual percent change in htTKV

was 1.94% per year greater in the metformin group ({-1.95, 5.99}, P=0.32); and the annual decline for eGFR was 1.58 ml/min/1.73m^2 greater ({-1.40, 4.55}; P=0.30) in the placebo arm.

Similar results held for the COVID-19 sensitivity analyses for GSRS and htTKV. GSRS did not significantly change over time (annual change = -0.04 {-0.06, -0.01} vs -0.01 {-0.04, 0.02}; P=0.15), and the mean annual percent change in htTKV was 1.78% per year greater in the metformin group ({-2.29, 6.02}, P=0.39). However, for eGFR, the annual decline was 0.25 ml/min/1.73m^2 greater ({-0.79, 1.34}; P=0.65) in the placebo arm, which was attenuated from the estimate of 1.37 in the ITT analysis.

Metabolic effects of metformin

Lactic acid levels were not different between treatment groups and did not change over time (Table S6). The annual change was 0.14 mmol/L (0.04, 0.23) for the metformin group and 0.05 (-0.05, 0.14) for the placebo group; the mean group difference was 0.09 (-0.05, 0.22), P=0.21. There were 25 (51%) participants taking metformin and 20 (42%) taking placebo with at least 1 lactic acid value that exceeded the upper limit of normal during the entire study. None of these were associated with clinical symptomatology or events, and repeat values returned to normal without any intervention.

We were unable to document hypoglycemia since potential episodes (otherwise unexplained symptoms of shakiness, dizziness, sweating, tachycardia or confusion) occurred off-site without immediate access to measurements of blood glucose. However, there were 10 episodes from 9 participants that were clinically consistent with hypoglycemia (4 metformin; 5 placebo); 4 of these episodes resulted in dose reductions (1 of which was metformin). Baseline eGFR appeared to be greater among the 4 metformin participants with possible hypoglycemia (102.5 ml/min/1.73m^2) versus the 5 placebo participants (82.5 ml/min/1.73m^2).

Vitamin B12 levels (Table S7) were required to be within the normal range at baseline and were supplemented if they fell below the normal range. Two participants (4%) receiving metformin and 2 participants (4%) on placebo required supplementation. The annual change was -46.85 (-91.78, -1.93) pg/ml in the metformin

group and -5.88 pg/ml (-49.72, 37.97) in the placebo group, resulting in the group difference (metformin minus placebo) of -40.98 (-103.76, 21.80} (P=0.20).

There was a significant difference in mean annual weight gain (kg) in the placebo group (1.01 {0.52, 1.50}) vs. the metformin group (-0.33 {-0.83, 0.18}), resulting in the group difference (metformin minus placebo) of -1.34 (-2.04, -0.63) (P<0.001).

Discussion

The results of the TAME PKD study demonstrate that the use of metformin in people aged 18 – 60 with ADPKD with eGFR $\geq$ 50 ml/min/1.73m^2 was feasible, safe and relatively well tolerated over a 24 month period. There were no significant safety issues.

Measures of tolerability included assessment of gastrointestinal symptoms using the GSRS scale and asking study participants "Can you tolerate this dose of the study drug for the rest of your life?" It is notable that values of the GSRS were very low at baseline, indicating minimal gastrointestinal symptomatology, and did not change throughout the study in either the metformin or placebo group; mean change in GSRS from baseline was 0.7 (0.7) for metformin and 0.1 (0.4) in placebo. Dose reduction or discontinuation of study medication was not significantly different between the metformin and placebo groups.

One of the potential concerns regarding the use of metformin in chronic kidney disease is the rare but severe complication of lactic acidosis. Dosing of metformin was reduced to no more than 500 mg twice daily for eGFR of $\geq$ 30 to $\leq$ 45 ml/min/1.73m^2 and discontinued for eGFR < 30 ml/min/1.73m^2. Lactic acid levels were closely monitored and were largely within the normal range. Hypoglycemia was suspected for several participants but not formally documented because of its occurrence outside the study sites. Nonetheless, there were 10 occurrences of clinical symptoms consistent with hypoglycemia evenly divided between metformin and placebo. Vitamin B12 levels remained within the normal range for most participants.

The TAME PKD study was designed as a phase 2 trial with endpoints evaluating the tolerability, safety, and preliminary efficacy of metformin in adults with ADPKD. Preliminary measures of efficacy including long-term impact on eGFR progression and total kidney and liver and cyst growth demonstrated the anticipated decline in eGFR, and growth in htTKV and htLV but no significant impact of metformin on these parameters. Decline of eGFR was numerically less in metformin than placebo but not statistically significant. Groupings of participants by high- vs. low-risk for progression status by imaging (using the Mayo Imaging Classification) or genetics

(using genotype) similarly did not demonstrate a signal of efficacy. Nonetheless, there was very low power to demonstrate such effects, particularly when groups were further subdivided, which does not preclude the possibility of detecting benefit in a larger trial of longer duration focused on participants with a higher risk of progression. A hypothetical phase 3 trial would necessitate 700-800 study participants in order to detect a 25% improvement in eGFR decline and 45% reduction in htTKV slope (further details are provided in the supplementary material).

A limitation in application of study results was the preponderance of female versus male participants and the preponderance of white participants. Unfortunately, lack of diversity is also reported in several other large intervention trials in ADPKD. [2, 3, 5, 6]

The choice of endpoints in clinical intervention trials for ADPKD has been extensively discussed by clinical trialists, industry sponsors, and regulators.[34] Use of eGFR as an endpoint in participants with preserved eGFR requires large trials of long duration because of the slow progression of eGFR in the early stages of ADPKD. Alternative clinical trial endpoints, particularly TKV, have been utilized to detect benefit at an earlier stage. Indeed, the US Food and Drug Administration has determined that TKV can be used both as a prognostic biomarker for selection of patients into clinical progression trials of ADPKD (prognostic enrichment)[35] and as a reasonably likely surrogate endpoint.[34] Design of a large, randomized trial of metformin in ADPKD presents several challenges. Because initiation of metformin is not advised at eGFR < 45 ml/min/1.73m^2, prognostic enrichment of study participants through imaging[33] or genetics[36] would be essential to allow detection of endpoints with sufficient power and manageable study duration.

It is anticipated that interventions that impact common pathophysiological mechanisms might simultaneously benefit both polycystic liver and kidney. Baseline kidney volume, eGFR, genetics, and Mayo image classification of the TAME population were reasonably well balanced between metformin and placebo groups.

However, there was a slight imbalance in liver volume and liver cyst volume between the groups. Stratification to provide balance for both kidney and liver volumes in a future study might make recruitment very challenging.

Tolvaptan was approved in April, 2018 and its availability did not impact initial recruitment. After approval of tolvaptan, the steering committee made the decision to exclude new participants taking tolvaptan and to exclude its use by previously randomized participants. Only 2 participants (1 metformin; 1 placebo) withdrew consent due to desire to take tolvaptan. Future intervention trials in ADPKD will need to consider the use of tolvaptan in study design.

In conclusion, the TAME PKD study has successfully determined safety and tolerability of metformin in ADPKD. The use of metformin in ADPKD with eGFR $\geq$ 50 ml/min/1.73m^2 is safe, and reasonably well tolerated. Lactic acidosis and hypoglycemia were not found to be problematic. No signal for efficacy to slow progression was evident. Future trials of metformin in ADPKD are feasible but will be enhanced with prognostic enrichment using TKV-based imaging classification.

Disclosures

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Dr. Bae is a consultant to Kadmon, Otsuka, and Sanofi.

Dr. Tao has nothing to declare.

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Drs. Abebe and Althouse and Ms. Lalama have nothing to declare.

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Tables

Table 1: Baseline Characteristics by Randomized Arm

Characteristic *	Metformin (n=49)	Placebo (n=48)
Age (years) (at Screening)	41.8 (10.4)	42.1 (10.1)
PKD genotype		
PKD1	37 (78.7%)	28 (60.9%)
PKD2	7 (14.9%)	10 (21.7%)
Other	1 (2.1%)	4 (8.7%)
No mutation detected	2 (4.3%)	4 (8.7%)
GFR calculated per CKD-EPI (ml/min/1.73 m²)	86.1 (20.6)	85.9 (19.0)
Vitamin B12 (pg/mL)	580.7 (350.8)	495.3 (202.3)
Glucose (mg/dL)	88.6 (8.4)	90.9 (9.1)
HbA1c (%)	5.2 (0.3)	5.2 (0.3)
Serum Creatinine (mg/dL)	0.9 (0.2)	0.9 (0.2)
Systolic BP (mmHg)	122.2 (13.1)	124.1 (13.0)
Diastolic BP (mmHg)	76.8 (8.9)	74.6 (8.5)
Weight (kg)	78.5 (16.9)	78.2 (17.4)
BMI	27.0 (5.9)	26.6 (4.5)
Gastrointestinal Symptoms Rating Scale, mean score	1.4 (0.5)	1.3 (0.4)
Reflux	1.6 (1.1)	1.4 (0.8)
Abdominal Pain	1.5 (0.7)	1.4 (0.6)
Indigestion	1.5 (0.6)	1.4 (0.5)
Diarrhea	1.2 (0.4)	1.2 (0.5)
Constipation	1.3 (0.6)	1.3 (0.5)
SF-36 MCS	51.7 (9.0)	53.1 (7.9)
SF-36 PCS	52.2 (6.5)	53.2 (6.3)
Mayo Imaging Class		
Class 2	2 (4.2%)	5 (10.4%)
Class 1A	9 (18.8%)	6 (12.5%)
Class 1B	13 (27.1%)	15 (31.3%)
Class 1C	14 (29.2%)	12 (25.0%)
Class 1D	6 (12.5%)	6 (12.5%)
Class 1E	4 (8.3%)	4 (8.3%)
Height-adjusted total kidney volume (mL/m)	625.8 (386.5)	750.9 (547.8)
Height-adjusted liver volume (mL/m)	1,224.1 (490.7)	1,019.0 (212.6)

** Continuous variables described as mean (SD) and categorical variables as n (%)*

Table 2: Serious Adverse Events

		Metformin * (n=49)		Placebo * (n=48)	
CTCAE Category	**CTCAE Event Term**	**n events**	**n (%) participants**	**n events**	**n (%) participants**
Overall (Chi-square p-value = 0.98)		**8**	**4 (8.2)**	**5**	**4 (8.3)**
Infections and infestations		**1**	**1 (2.0)**	**2**	**2 (4.2)**
	Appendicitis perforated	0	0	1	1 (2.1)
	Other - diarrhea (c. difficile infection)	1	1 (2.0)	0	0
	Other - urinary tract infection and renal cyst hemorrhage (mild)	0	0	1	1 (2.1)
Musculoskeletal and connective tissue disorders		**2**	**1 (2.0)**	**0**	**0**
	Other - bone fracture	1	1 (2.0)	0	0
	Other - fall with bone fracture	1	1 (2.0)	0	0
Nervous system disorders		**1**	**1 (2.0)**	**1**	**1 (2.1)**
	Other - lightheadedness	0	0	1	1 (2.1)
	Seizure	1	1 (2.0)	0	0
Renal and urinary disorders		**0**	**0**	**2**	**2 (4.2)**
	Other - renal cyst hemorrhage	0	0	1	1 (2.1)
	Other - renal cyst rupture	0	0	1	1 (2.1)
Gastrointestinal disorders		**1**	**1 (2.0)**	**0**	**0**
	Gastric hemorrhage	1	1 (2.0)	0	0
Psychiatric disorders		**1**	**1 (2.0)**	**0**	**0**
	Suicide attempt	1	1 (2.0)	0	0
Surgical and medical procedures		**1**	**1 (2.0)**	**0**	**0**
	Other - umbilical hernia	1	1 (2.0)	0	0
Vascular disorders		**1**	**1 (2.0)**	**0**	**0**
	Hematoma	1	1 (2.0)	0	0

* *Includes randomized participants who at least received and took metformin or placebo.*

Table 3: Height-adjusted Total Kidney Volume

	htTKV n mean (95% CI)	
Study Visit	**Metformin**	**Placebo**
Baseline	48 625.8 (513.6, 738.1)	48 750.9 (591.8, 909.9)
F6	43 596.3 (498.5, 694.1)	44 764.1 (590.8, 937.4)
F12	42 620.9 (516.2, 725.6)	43 789.9 (613.1, 966.7)
F18	38 665.6 (547.8, 783.4)	42 822.1 (637.7, 1,006.5)
F24	35 706.7 (575.8, 837.7)	38 853.6 (649.0, 1,058.2)

ln(htTKV) % per year (95% CI)		
Metformin	**Placebo**	**Metformin vs. Placebo**
3.87 (1.09, 6.74)	2.16 (-0.52, 4.91)	1.68 (-2.11, 5.62) P=0.38

htTKV: height-adjusted total kidney volume
ln(htTKV): natural log-transformed htTKV

Table 4: Height-adjusted Liver Volume

	htLV n mean (95% CI)	
Study Visit	**Metformin**	**Placebo**
Baseline	48 1,224.1 (1,081.6, 1,366.6)	48 1,019.0 (957.3, 1,080.8)
F6	43 1,307.0 (1,114.8, 1,499.2)	44 1,020.9 (955.5, 1,086.3)
F12	42 1,311.3 (1,120.5, 1,502.0)	43 1,042.7 (974.1, 1,111.3)
F18	38 1,353.8 (1,139.4, 1,568.3)	42 1,048.4 (976.7, 1,120.1)
F24	35 1,375.1 (1,143.8, 1,606.4)	38 1,075.4 (993.3, 1,157.5)

ln(htLV) % per year (95% CI)		
Metformin	**Placebo**	**Metformin vs. Placebo**
1.60 (0.02, 3.21)	1.21 (-0.32, 2.77)	0.39 (-1.78, 2.61) P=0.72

htLV: height-adjusted liver volume
ln(htLV): natural log-transformed htLV

Table 5: Health-related Quality of Life

	SF-36 MCS n mean (95% CI)		SF-36 PCS n mean (95% CI)	
Study Visit	**Metformin**	**Placebo**	**Metformin**	**Placebo**
Baseline	49 51.7 (49.2, 54.3)	48 53.1 (50.8, 55.4)	49 52.2 (50.3, 54.1)	48 53.2 (51.3, 55.0)
F1	45 51.6 (48.4, 54.8)	47 51.8 (49.3, 54.4)	45 52.5 (50.7, 54.3)	47 53.8 (51.7, 55.9)
F3	44 51.7 (48.4, 55.0)	47 51.9 (48.9, 54.8)	44 52.0 (50.2, 53.9)	47 53.1 (50.8, 55.3)
F6	43 50.3 (47.1, 53.6)	45 51.9 (49.4, 54.3)	43 53.1 (51.2, 55.0)	45 52.4 (50.2, 54.6)
F9	42 50.5 (47.5, 53.5)	44 53.7 (51.6, 55.9)	42 52.1 (50.2, 54.0)	44 52.7 (50.8, 54.7)
F12	42 52.1 (49.5, 54.7)	42 54.1 (51.7, 56.5)	42 51.7 (49.9, 53.4)	42 51.6 (49.5, 53.8)
F15	42 50.4 (47.5, 53.3)	43 52.7 (50.3, 55.1)	42 52.1 (49.9, 54.4)	43 52.5 (50.9, 54.1)
F18	42 51.4 (48.2, 54.7)	43 51.7 (49.1, 54.4)	42 51.3 (49.0, 53.6)	43 52.7 (50.7, 54.6)
F21	41 51.1 (48.3, 53.9)	42 51.2 (48.4, 54.1)	41 52.8 (51.1, 54.4)	42 52.4 (50.4, 54.5)
F24	39 52.2 (49.7, 54.7)	42 53.0 (50.9, 55.0)	39 52.1 (50.1, 54.0)	42 52.3 (50.0, 54.6)
F26	39 53.3 (50.7, 55.9)	45 53.2 (51.2, 55.1)	39 51.4 (49.0, 53.8)	45 53.3 (51.4, 55.3)

SF-36 MCS mean annual change (95% CI)			SF-36 PCS mean annual change (95% CI)		
Metformin	**Placebo**	**Metformin vs. Placebo**	**Metformin**	**Placebo**	**Metformin vs. Placebo**
0.51 (-0.62, 1.63)	-0.06 (-1.15, 1.04)	0.56 (-12.01, 2.13) P=0.49	-0.06 (-0.85, 0.73)	-0.26 (-1.03, 0.52)	0.20 (-0.91, 1.30) P=0.72

Table 6: Pain Frequency in Prior 3 Months

		Back Pain n (%)		Abdominal Fullness* n (%)	
Study Visit	**Frequency**	**Metformin**	**Placebo**	**Metformin**	**Placebo**
Baseline	**Never, Rarely, Sometimes**	33 (67.3%)	35 (72.9%)	47 (95.9%)	48 (100.0%)
	Often, Usually, Always	16 (32.7%)	13 (27.1%)	2 (4.1%)	0 (0.0%)
F1	**Never, Rarely, Sometimes**	34 (75.6%)	37 (78.7%)	45 (100.0%)	46 (97.9%)
	Often, Usually, Always	11 (24.4%)	10 (21.3%)	0 (0.0%)	1 (2.1%)
F3	**Never, Rarely, Sometimes**	33 (75.0%)	38 (80.9%)	42 (95.5%)	47 (100.0%)
	Often, Usually, Always	11 (25.0%)	9 (19.1%)	2 (4.5%)	0 (0.0%)
F6	**Never, Rarely, Sometimes**	33 (76.7%)	36 (80.0%)	43 (100.0%)	44 (97.8%)
	Often, Usually, Always	10 (23.3%)	9 (20.0%)	0 (0.0%)	1 (2.2%)
F9	**Never, Rarely, Sometimes**	35 (83.3%)	35 (79.5%)	40 (95.2%)	44 (100.0%)
	Often, Usually, Always	7 (16.7%)	9 (20.5%)	2 (4.8%)	0 (0.0%)
F12	**Never, Rarely, Sometimes**	36 (85.7%)	35 (83.3%)	42 (100.0%)	41 (97.6%)
	Often, Usually, Always	6 (14.3%)	7 (16.7%)	0 (0.0%)	1 (2.4%)
F15	**Never, Rarely, Sometimes**	31 (73.8%)	38 (88.4%)	41 (97.6%)	42 (97.7%)
	Often, Usually, Always	11 (26.2%)	5 (11.6%)	1 (2.4%)	1 (2.3%)
F18	**Never, Rarely, Sometimes**	35 (83.3%)	35 (81.4%)	41 (97.6%)	41 (95.3%)
	Often, Usually, Always	7 (16.7%)	8 (18.6%)	1 (2.4%)	2 (4.7%)
F21	**Never, Rarely, Sometimes**	34 (82.9%)	33 (78.6%)	39 (95.1%)	41 (97.6%)
	Often, Usually, Always	7 (17.1%)	9 (21.4%)	2 (4.9%)	1 (2.4%)
F24	**Never, Rarely, Sometimes**	31 (79.5%)	34 (81.0%)	39 (100.0%)	42 (100.0%)
	Often, Usually, Always	8 (20.5%)	8 (19.0%)	0 (0.0%)	0 (0.0%)
F26	**Never, Rarely, Sometimes**	34 (87.2%)	40 (87.0%)	38 (97.4%)	45 (100.0%)
	Often, Usually, Always	5 (12.8%)	6 (13.0%)	1 (2.6%)	0 (0.0%)

Back Pain OR per month (95% CI)			Abdominal Fullness* OR per month (95% CI)		
Metformin	**Placebo**	**Metformin vs. Placebo**	**Metformin**	**Placebo**	**Metformin vs. Placebo**
0.95 (0.90, 1.00)	0.92 (0.88, 0.98)	P=0.44	1.00 (0.89, 1.13)	0.99 (0.87, 1.12)	P=0.83

* *Specifically, how often did abdominal fullness interfere with ability to perform usual physical acitivities*

Table 7: Pain Interference in Prior 3 Months

		Sleep n (%)		Strenuous Physical Activity n (%)	
Study Visit	**Frequency**	**Metformin**	**Placebo**	**Metformin**	**Placebo**
Baseline	**Not at all, A little bit, Moderately**	44 (89.8%)	47 (97.9%)	43 (87.8%)	44 (91.7%)
	Quite a bit, Extremely	5 (10.2%)	1 (2.1%)	6 (12.2%)	4 (8.3%)
F1	**Not at all, A little bit, Moderately**	44 (97.8%)	46 (97.9%)	40 (88.9%)	45 (95.7%)
	Quite a bit, Extremely	1 (2.2%)	1 (2.1%)	5 (11.1%)	2 (4.3%)
F3	**Not at all, A little bit, Moderately**	42 (95.5%)	46 (97.9%)	38 (86.4%)	40 (85.1%)
	Quite a bit, Extremely	2 (4.5%)	1 (2.1%)	6 (13.6%)	7 (14.9%)
F6	**Not at all, A little bit, Moderately**	40 (93.0%)	44 (97.8%)	38 (88.4%)	42 (93.3%)
	Quite a bit, Extremely	3 (7.0%)	1 (2.2%)	5 (11.6%)	3 (6.7%)
F9	**Not at all, A little bit, Moderately**	36 (85.7%)	43 (97.7%)	35 (83.3%)	44 (100.0%)
	Quite a bit, Extremely	6 (14.3%)	1 (2.3%)	7 (16.7%)	0 (0.0%)
F12	**Not at all, A little bit, Moderately**	40 (95.2%)	41 (97.6%)	37 (88.1%)	39 (92.9%)
	Quite a bit, Extremely	2 (4.8%)	1 (2.4%)	5 (11.9%)	3 (7.1%)
F15	**Not at all, A little bit, Moderately**	39 (92.9%)	41 (95.3%)	39 (92.9%)	41 (95.3%)
	Quite a bit, Extremely	3 (7.1%)	2 (4.7%)	3 (7.1%)	2 (4.7%)
F18	**Not at all, A little bit, Moderately**	40 (95.2%)	41 (95.3%)	36 (85.7%)	38 (88.4%)
	Quite a bit, Extremely	2 (4.8%)	2 (4.7%)	6 (14.3%)	5 (11.6%)
F21	**Not at all, A little bit, Moderately**	39 (95.1%)	41 (97.6%)	38 (92.7%)	37 (88.1%)
	Quite a bit, Extremely	2 (4.9%)	1 (2.4%)	3 (7.3%)	5 (11.9%)
F24	**Not at all, A little bit, Moderately**	36 (92.3%)	41 (97.6%)	36 (92.3%)	37 (88.1%)
	Quite a bit, Extremely	3 (7.7%)	1 (2.4%)	3 (7.7%)	5 (11.9%)
F26	**Not at all, A little bit, Moderately**	37 (94.9%)	43 (95.6%)	36 (92.3%)	41 (91.1%)
	Quite a bit, Extremely	2 (5.1%)	2 (4.4%)	3 (7.7%)	4 (8.9%)

Sleep OR per month (95% CI)			Strenuous Physical Activity OR per month (95% CI)		
Metformin	**Placebo**	**Metformin vs. Placebo**	**Metformin**	**Placebo**	**Metformin vs. Placebo**
1.00 (0.87, 1.14)	0.97 (0.88, 1.07)	P=0.72	0.99 (0.93, 1.06)	0.95 (0.90, 1.01)	P=0.28

Figure Legends

Figure 1 Patient Enrollment and Outcomes

We screened 108 patients, of whom 97 were randomly assigned to receive either metformin or placebo. Overall, 82 patients (84.5%) completed the 2-year trial. The Intention To Treat analyses included all 97 patients for safety, tolerability, and preliminary efficacy outcomes.

Figure 2 Gastrointestinal Symptom Rating Scale (GSRS)

The full range of the GSRS scale is shown for the mean score and all 5 subdomains: abdominal pain, diarrhea, reflux, indigestion and constipation. The mean annual change (95% CI) was: Metformin -0.02 (-0.09, 0.05); placebo -0.06 (-0.12, 0.02), metformin vs. placebo 0.04 (-0.07, 0.13); P=0.50. Symbols represent means and □ bars 95% confidence intervals

Figure 3 Height-adjusted Total Kidney Volume

htTKV values of each study visit are shown for metformin and placebo groups. The annual percent change was: Metformin 3.87 (1.09, 6.74) %, Placebo 2.16 (-0.52, 4.91) %, Metformin vs. Placebo 1.68 (-2.11, 5.62) %; P=0.38; P=0.20. Symbols represent means and □ bars 95% confidence intervals

Figure 4 eGFR

eGFR values for each study visit are shown in ml/min/1.73m^2 for metformin and placebo groups.

The mean annual change was: Metformin -1.71 (-3.18, -0.23) ml/min/1.73m^2, Placebo -3.07 (-4.52, -1.62) ml/min/1.73m^2, Metformin vs. Placebo 1.37 (-0.70, 3.44) ml/min/1.73m^2; P=0.20. Symbols represent means and □ bars 95% confidence intervals

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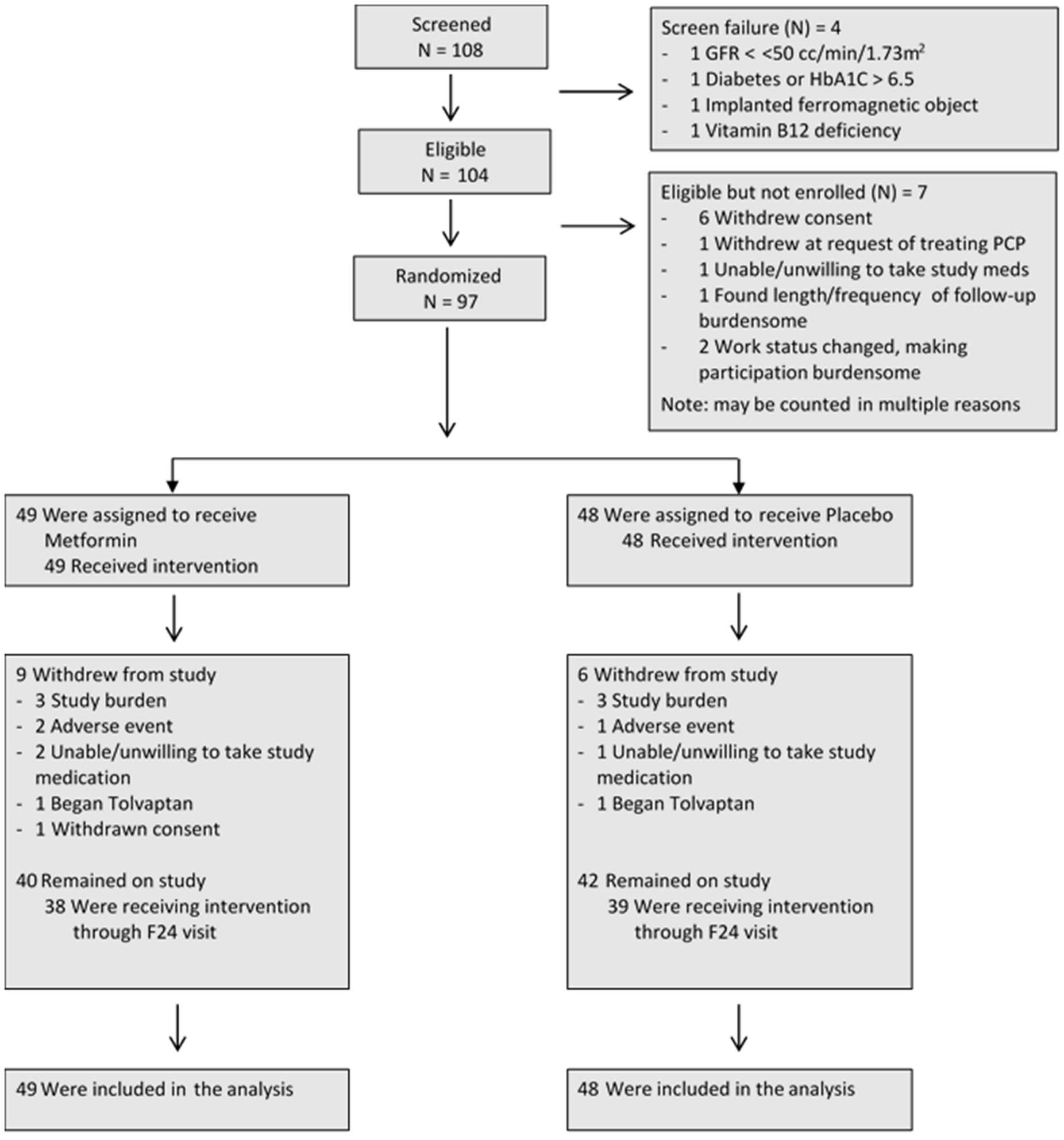
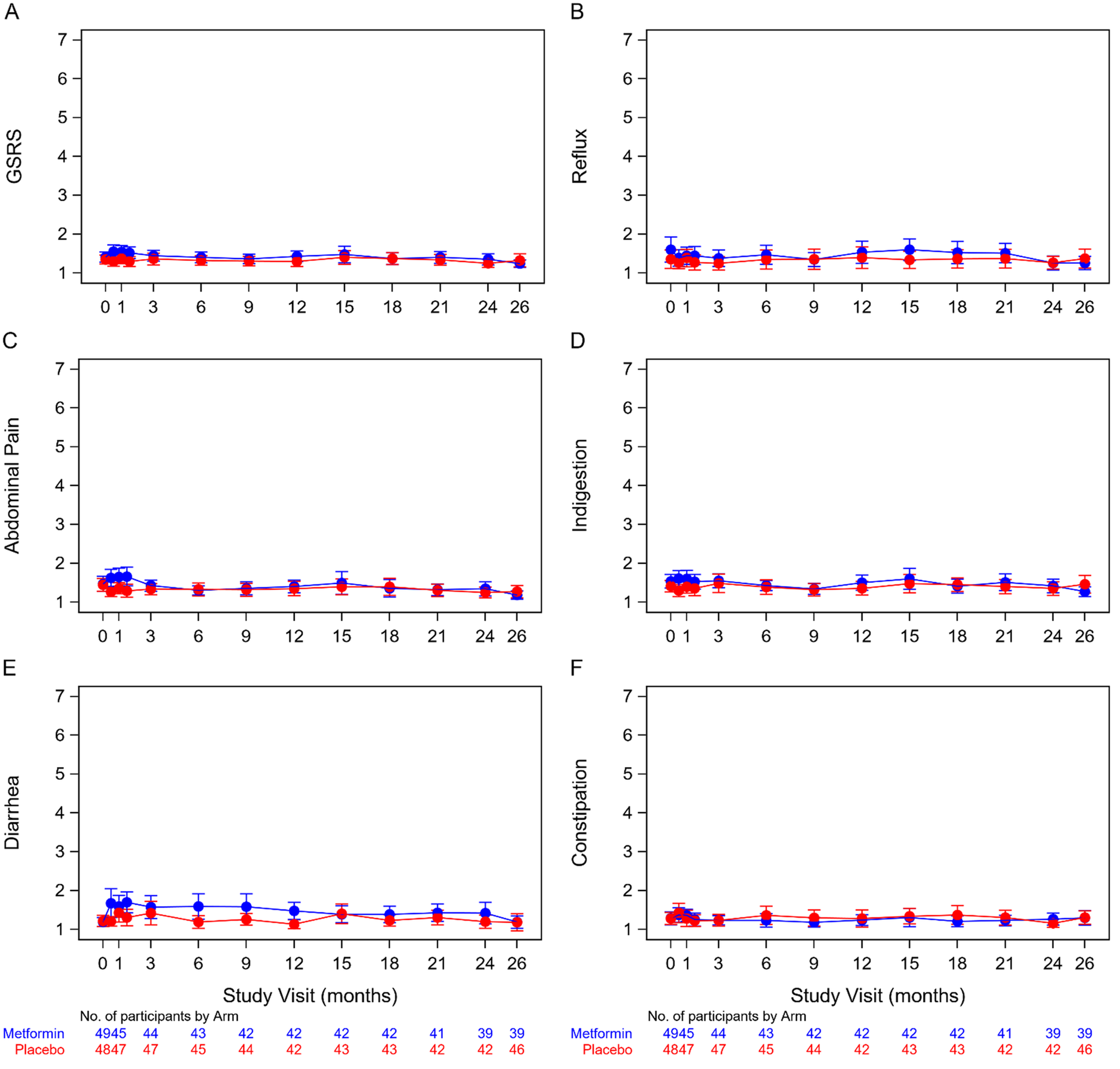
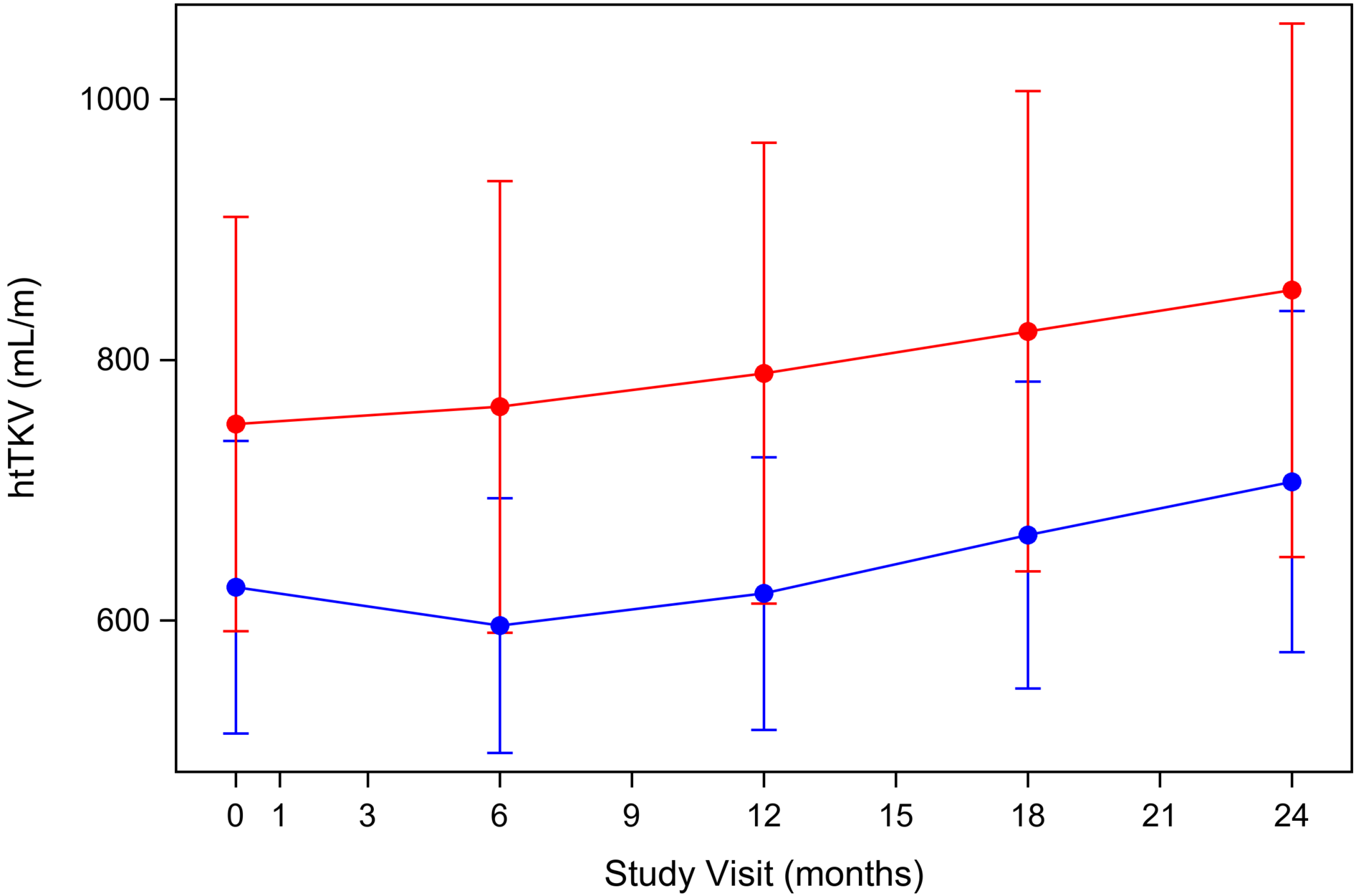
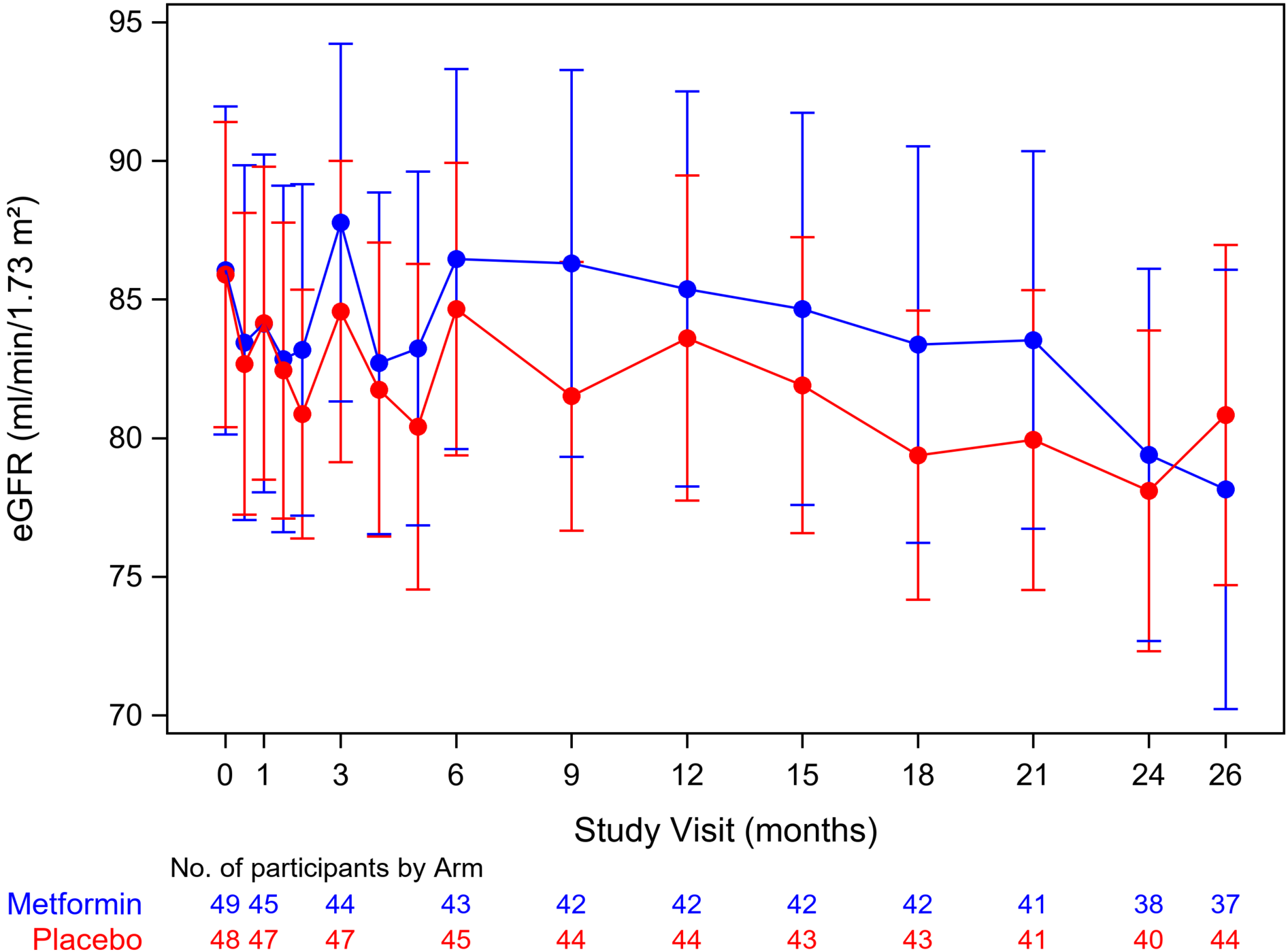

Screened
N = 108
Screen failure (N) = 4
- 1 GFR < <50 cc/min/1.73m²
- 1 Diabetes or HbA1C > 6.5
- 1 Implanted ferromagnetic object
- 1 Vitamin B12 deficiency
Eligible
N = 104
Eligible but not enrolled (N) = 7
- 6 Withdrew consent
- 1 Withdrew at request of treating PCP
- 1 Unable/unwilling to take study meds
- 1 Found length/frequency of follow-up burdensome
- 2 Work status changed, making participation burdensome
Note: may be counted in multiple reasons
Randomized
N = 97
49 Were assigned to receive Metformin
49 Received intervention
48 Were assigned to receive Placebo
48 Received intervention
9 Withdrew from study
- 3 Study burden
- 2 Adverse event
- 2 Unable/unwilling to take study medication
- 1 Began Tolvaptan
- 1 Withdrawn consent
40 Remained on study
38 Were receiving intervention through F24 visit
6 Withdrew from study
- 3 Study burden
- 1 Adverse event
- 1 Unable/unwilling to take study medication
- 1 Began Tolvaptan
42 Remained on study
39 Were receiving intervention through F24 visit
49 Were included in the analysis
48 Were included in the analysis


A
GSRS
B
Reflux
C
Abdominal Pain
D
Indigestion
E
Diarrhea
F
Constipation
1
2
3
4
5
6
7
0 1 3 6 9 12 15 18 21 24 26
Study Visit (months)
No. of participants by Arm
Metformin 4945 44 43 42 42 42 42 41 39 39
Placebo 4847 47 45 44 42 43 43 42 42 46


1000
800
600
htTKV (mL/m)
0
1
3
6
9
12
15
18
21
24
Study Visit (months)
No. of participants by Arm
Metformin 48 43 42 38 35
Placebo 48 44 43 42 38


95
90
85
80
75
70
eGFR (ml/min/1.73 m²)
0
1
3
6
9
12
15
18
21
24
26
Study Visit (months)
No. of participants by Arm
Metformin 49 45 44 43 42 42 42 42 41 38 37
Placebo 48 47 47 45 44 44 43 43 41 40 44

Primary results of the randomized trial of metformin administration in polycystic kidney disease (TAME PKD).

kidney INTERNATIONAL

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Phase 2 randomized trial:

97

Patients aged 18-60 with autosomal dominant polycystic kidney disease **(ADPKD)**

49 metformin

48 placebo

Estimated Glomerular Filtration Rate: **eGFR≥** 50ml/min/1.73m^2

Primary Outcomes

Medication safety

No difference in:

- adverse events
- lactate levels
- potential hypoglycemia

Tolerability

Inability to tolerate, reduced dose:

- 21 MET participants (43%)
- 14 PLC (29%)

Gastrointestinal Symptom Rating Score (GSRS)

- low at baseline
- did not significantly change over time

Secondary Outcomes

eGFR Decline

Annual change

- -1.71 in MET
- -3.07 ml/min/1.73m^2 in PLC

Total Kidney Volume (TKV) Growth by MRI

Mean annual % change in height-adjusted TKV

- 3.87% in MET
- 2.16% in PLC

Perrone RD et al, 2021

Conclusion: ***Metformin in adults with ADPKD is safe and tolerable. Evaluation of efficacy will require a larger clinical trial, with sufficient power to detect differences in endpoints.***