Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Contents

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Supplementary Statistical Methods

A. Study Estimands

To elucidate the target of the research question, we followed the ICH E9 (R1) addendum guidelines (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e9r1-statistical-principles-clinical-trials-addendum-estimands-and-sensitivity-analysis-clinical) and specified study *estimands* in terms of four attributes defining the treatment effect of interest. Specifically, for the ***primary*** estimand, these attributes were defined as follows:

1. *Target population* consists of persons with type 1 diabetes that meets the inclusion/exclusion criteria.

2. *The endpoint of interest obtained for each patient that addresses the scientific question of interest* is the measured glomerular filtration rate (iGFR) based on plasma disappearance of non-radioactive iohexol at the end of the 2-month wash-out period (visit V17 at Week 164) following the 3-year treatment.

3. *Strategies for addressing intercurrent (IC) events*.
To describe these strategies, we grouped various intercurrent events that occurred in the PERL study based on their implications for subsequent data collection of the primary endpoint (see Table A). Depending on the IC event group, iGFR values collected *after* an IC event were considered as follows:

(a) Group A IC events were considered as directly interpretable. Effectively, IC events in this group are *ignored*, in agreement with the intention-to-treat (ITT) principle.

(b) Group B IC events were assumed to follow a *hypothetical* scenario, in which iGFR values after developing ESKD take on biologically plausible values that are not confounded by the IC event, i.e., by ESKD treatments such as dialysis or kidney transplant.

(c) Group C IC events were assumed to conform to a *hypothetical* scenario, in which post-IC iGFR values have a similar distribution to other non-ESKD subjects with similar characteristics and pre-IC iGFR values.

4. *The population summary for the endpoint that provides a basis for a comparison between treatment conditions* is the population-average treatment effect on iGFR at visit V17 (Week 164).

Table A. Groups of intercurrent (IC) events in PERL study

Group of IC events	**IC event**	**Consequences for collecting post-IC event data applicable to all estimands**	**Implications for the analysis of *primary estimand***
Group A	Non-adherence to study drug schedule	Post-IC event data are collected, but their interpretation may be affected depending on the	Post-IC event iGFR values are directly interpretable and included in the
	Permanent discontinuation of		

	study drug	estimand of interest	analysis
	Use of prohibited medication		
	Missed scheduled visit		
Group B	ESKD diagnosis or treatment (hemodialysis or transplant)	Post-IC event data do not contain any relevant information about estimands of interest and for this reason they are not collected	Post-IC event iGFR values are imputed under missing not at random (MNAR) assumption
Group C	Early discontinuation from the study	Post-IC event data cannot be collected	Post-IC event iGFR values are imputed under missing at random (MAR) assumption
	Terminal event, i.e., death		

Secondary estimands were defined in a similar fashion for the secondary endpoints listed below and are described in the Statistical Analysis Plan. Secondary endpoints include:

1. Baseline-adjusted iGFR at the end of treatment
2. Baseline-adjusted eGFR at 4 mo. from randomization
3. iGFR slope (ml per min per 1.73 m^2 per year)
4. eGFR slope (ml per min per 1.73 m^2 per year)
5. Urinary AER at the end of wash-out
6. Urinary AER at the end of treatment
7. Time to serum creatinine doubling or ESKD
8. Time to fatal or non-fatal cardiovascular event

B. Missing Values

To limit the impact of missing values, we undertook several precautions and employed ideas pertaining to study design, conduct, analysis and inference presented in Little et al.[1] In terms of the analysis of the main endpoint, to effectively address missing values in baseline covariates and post-randomization variables of interest, and to appropriately cast post-ESKD iGFR values as an unfavorable outcome, we used one of the recommended approaches, namely a *multiple imputation* (MI) approach. This consisted of three steps:

Step 1. Using an *imputation* model, create 25 dataset instances with missing values imputed.

Step 2. Fit *analytic models* to the imputed datasets created in Step 1.

Step 3. For each analytic model, combine the results obtained in Step 2 for statistical inference using Rubin's rule[2].

Multivariate imputation using the fully conditional specification (FCS) method[3] was employed in Step 1. The *imputation* model employed a regression method for continuous dependent variables and a discriminant function method for categorical dependent variables. In both cases, all

continuous variables involved in the imputation, *except* dependent variables, were used as covariates. Variables in the imputation model included baseline covariates that are used in the analytic models, screening HbA1c, eGFR, iGFR and AER (expressed on the logarithmic base 10 scale) at all post-randomization visits. Imputation of baseline variables was performed starting with variables having the lowest number of missing values (Table B). Variables measured longitudinally (i.e., eGFR, iGFR, AER) were modeled sequentially in the order determined by the visit number. To preserve different response trajectories in the study treatment groups (i.e., treatment group by study visit interaction), imputations were performed separately in each treatment group. We note that the FCS method imputes data under the missing at random (MAR) assumption, e.g., the probability that the iGFR, eGFR or AER value is missing depends on *observed* rather than *unobserved* values of the variables. Although we consider the MAR assumption to be sensible for our study, it does not apply to post-ESKD iGFR and eGFR values.

Table B. Missingness of baseline covariates.

Baseline covariates	**N**	**%**
Serum urate	0	0.0%
eGFR	0	0.0%
iGFR	1	0.2%
HbA1c	2	0.4%
AER	2	0.4%
Kidney phenotype	12	2.3%

eGFR = estimated GFR (serum creatinine based); iGFR = iohexol-GFR, HbA1c = hemoglobin A1c; AER = albumin excretion rate

The imputation of *post-ESKD eGFR* measures was modeled according to the following criteria: (1) assigning a biologically acceptable value close to 7 ml/min/1.73 m^2, with a small amount of variation, (2) representing 'the worst-case scenario', and (3) reflecting the 'absorbing state' feature of ESKD. To this end, we imputed these values using a controlled imputation technique, specifically, the delta-adjustment approach[4]. More precisely to meet the requirements imposed on the imputed values, we *adjusted* imputed post-ESKD eGFR values by rescaling them by a factor of 0.01 and adding 7 ml/min/1.73 m^2. Details of this method are described in[5]. We note that eGFR measures are taken at every visit and are used to determine the time of developing ESKD. Hence, pre-ESKD eGFR values are highly predictive of post-ESKD iGFR values. In addition, we note that post-ESKD iGFR and eGFR values lie in a very narrow range and they are effectively interchangeable. For these reasons, we imputed post-ESKD iGFR values by using the corresponding post-ESKD eGFR imputed values as proxies.

The multiple imputation approach outlined above was applied to the analysis for the primary estimand and all secondary endpoints, except for the analyses involving time to event, such as time to serum creatinine doubling or ESKD and time to fatal or non-fatal cardiovascular event. Given relatively small number of subjects with missing values in covariates (n=17, 3.3%), the two aforementioned analyses were performed using a complete case approach.

C. Analysis of the Primary Estimand

The *primary* analysis for the primary estimand was performed in a multiple imputation (MI) framework on the intention-to-treat (ITT) sample and employed a linear model for correlated errors with general/unstructured covariance matrix, also known as mixed-effects model repeated measures (MMRM), as the analytical model. For each time t ($t = 1, 2, 3$) corresponding to post-randomization iGFR visits, i.e. visits V11 (80 weeks), V16 (156 weeks), and V17 (164 weeks after randomization) the model equation is specified as:

$$\text{iFR}_{\text{it}} = \beta_{0t} + \beta_{1t}\,\text{TRT}_i + \mathbf{x}_i'\boldsymbol{\beta} + \epsilon_{it}, \qquad (1)$$

where iFR_{it} is the value of iGFR at time t for subject i ($i = 1, \ldots, 530$). Fixed effects β_{0t}, β_{1t} for $t = 1, 2, 3$ denote visit-specific intercepts and treatment effects. TRT_i is treatment group (equal to 1 for the allopurinol and 0 for placebo). Stratifying variables (serum uric acid, HbA1c, study center), and baseline covariates: albuminuria status, AER, iGFR for subject i are included in a vector $\mathbf{x}_i$ of p covariates $(x_1, \ldots, x_p)$ and associated fixed effects are stored in vector $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_p)$. We assume that residual errors ϵ_{it} $(t = 1, 2, 3)$ for subject i are normally distributed with zero mean and 3x3 general/unstructured variance-covariance matrix. The model specified in (1) will yield the estimates of visit-specific treatment effects $\beta_{11}, \beta_{12}, \beta_{13}$ for all three visits V11, V16 and V17. In the context of the primary analysis of the primary endpoint, we are interested in parameter β_{13}, representing treatment effect at endpoint visit V17 adjusted for stratifying variables and baseline covariates. The Kenward-Roger approximation was used to estimate denominator degrees of freedom.

D. Tipping Point Sensitivity Analysis

Robustness of the results was assessed through a tipping point sensitivity analysis[4] within the same MI framework. We applied a marginal delta-adjusted method to the endpoint visit, increasing the imputed iGFR values by one unit for subjects in the allopurinol arm until the results of the primary analysis were overturned. Results showed that increasing imputed iGFRs in subjects from allopurinol group by 1 ml/min/1.73 m^2 increases the treatment effect by 0.23 ml/min/1.73 m^2 (Table C). Increasing the imputed iGFRs by 9 ml/min/1.73 m^2 overturns the conclusion of not finding evidence of a treatment effect (p=0.99) to that of detecting evidence of an effect (p=0.043) (Table C).

Table C. Tippint Point Sensitivity Analysis for the Primary Outcome: Results from Marginal Delta-Adjusted Method Applied to Endpoint Visit Only. ITT Analysis Set (Multiple Imputation).

Delta applied to endpoint visit for subjects in allopurinol arm	Treatment Effect (Allopurinol-Placebo)	Standard Error (SE)	P-Value
No adjustment	0.001	1.0	0.99
1 ml/min/1.73 m^2	0.2	1.0	0.82
2 ml/min/1.73 m^2	0.5	1.0	0.64
3 ml/min/1.73 m^2	0.7	1.0	0.49
4 ml/min/1.73 m^2	0.9	1.0	0.36

Delta applied to endpoint visit for subjects in allopurinol arm	Treatment Effect (Allopurinol-Placebo)	Standard Error (SE)	P-Value
5 ml/min/1.73 m^2	1.2	1.0	0.25
6 ml/min/1.73 m^2	1.4	1.0	0.17
7 ml/min/1.73 m^2	1.6	1.0	0.11
8 ml/min/1.73 m^2	1.8	1.0	0.071
9 ml/min/1.73 m^2	2.1	1.0	0.043
We assess the impact of deviations from the missing at random (MAR) assumption on the robustness of the results through a sensitivity analysis. The same multiple imputation and modeling framework is used for the primary estimand, however, we employ the marginal delta-adjusted method and added an adjustment (delta) to imputed visit V17 iGFR values only in the allopurinol arm. We increase the delta by one unit of iGFR (ml/min/1.73m^2) until the MAR results are overturned, that is, we use the so-called tipping point approach[4].			

Secondary analyses of the primary endpoint included an analysis of covariance and an analysis identical to the primary one but limited to the per-protocol analysis set. Results are presented in terms of adjusted iGFR means; estimate, 95% CI and p-value for the treatment effect at the last visit.

Completeness of iGFR Measurements

Table D provides a summary of the iGFR measurements performed during the study. iGFR tests were perfomed at 1,789 (97.9%) of 1,828 visits at which an iGFR test was part of the protocol. The few cases in which an IGFR was not performed (n=39, 2.1%) were due to extreme difficulties in venous access or conditions that made iGFR contraindicated, including 3 cases of ESKD that were diagnosed at the visit by eGFR just before the iGFR was to begin. Of the 1,789 iGFR tests that were performed, 1,768 (98.8%) yielded a valid value (1,729 at the 1st attempt and 39 at the 2nd attempt). The number of failures (n=21, 1.2%) would have been even lower, had the repetition of any invalid iGFR at week 156 not be hindered by the temporal proximity to the final visit at week 164. Altogether, there were 17 missing iGFR at V17, 3 due to a diagnosis of ESKD at that visit. These were in addition to those missing because of study discontinuations (n=108, Figure 1).

Table D. iGFR Measurements During the PERL Study.

	Week 0 (V4)	Week 80 (V11)	Week 156* (V16)	Week 164** (V17)	Total
Visits, N	530	467	409	422	1828
iGFRs performed, N (%)	530 (100)	459 (98.3)	389 (95.1)	411 (97.4)	1789 (97.9)
Valid iGFRs, N (%)	529 (99.8)	454 (98.9)	380 (97.7)	405 (98.8)	1768 (98.8)
1st attempt, N (%)	499 (94.3)	448 (98.7)	380 (97.7)	402 (99.3)	1729 (97.8)
2nd attempt, N (%)	30 (5.7)	6 (1.3)	NA*	3 (0.7)	39 (2.2)
Invalid iGFRs, N (%)	1 (0.2)	5 (1.1)	9 (2.3)	6 (1.5%)	21 (1.2)
iGFRs not performed, N (%)	0 (0.0%)	8 (1.7%)	20 (5.1%)*	11 (2.7%)**	39 (2.1)

iGFRs were considered to be valid if the regression between log-transformed iohexol values and the time at which they were obtained during the test had an R^2>0.90 and a negative slope. In the case of an invalid value, iGFRs were repeated within 4 weeks from when the iGFR results became available.

* In order to increase the likelihood of a successful iGFR at the final visit (V17, Week 164), sites were allowed to file a request for a prospective protocol deviation in order not to perform an iGFR at visit V16 (Week 156) if a participant had previously shown very difficult venous access, if a repeat visit 16 iGFR was too close in time to visit V17, or if sites deemed that a repeat visit V16 iGFR might discourage the participant from undergoing the visit V17 iGFR.

**Includes 3 subjects who were found to have reached ESKD at this visit and therefore did not undergo the scheduled iGFR.

Figure S1. Disposition of Study Participants During the Trial.

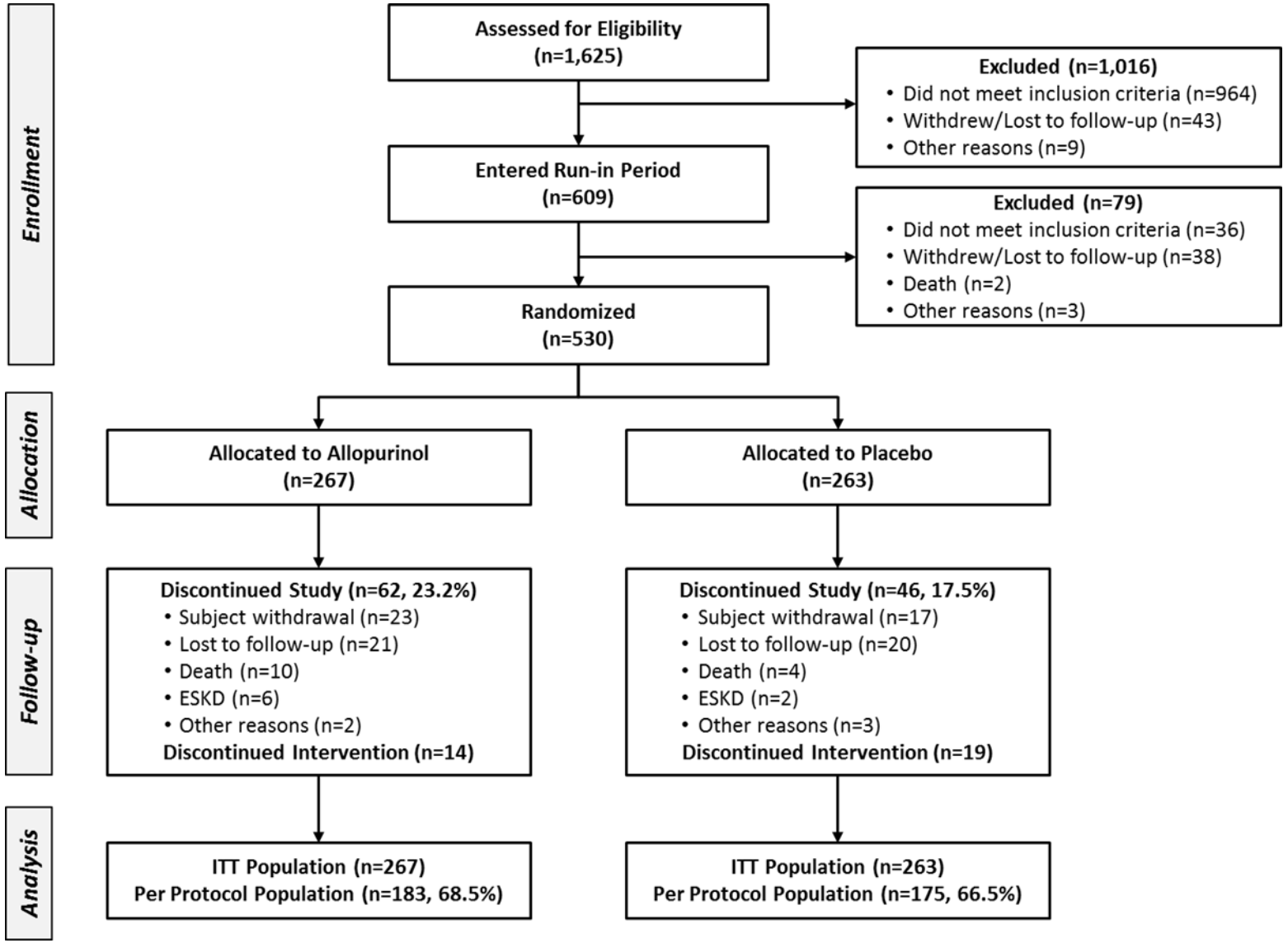

Figure S2. HbA1C, BMI, Systolic Blood Pressure, and Diastolic Blood Pressure During the Trial. Mean levels of HbA1c (Panel A), BMI (Panel B), systolic blood pressure (Panel C), and diastolic blood pressure (Panel D) in the two treatment groups are shown at different time points during the trial, along with their 95% confidence intervals. The red line corresponds to the allopurinol group, the blue line to the placebo group. Mean values refer to the participants with available data at each time point. Treatment with the study drug ended at week 156 since randomization.

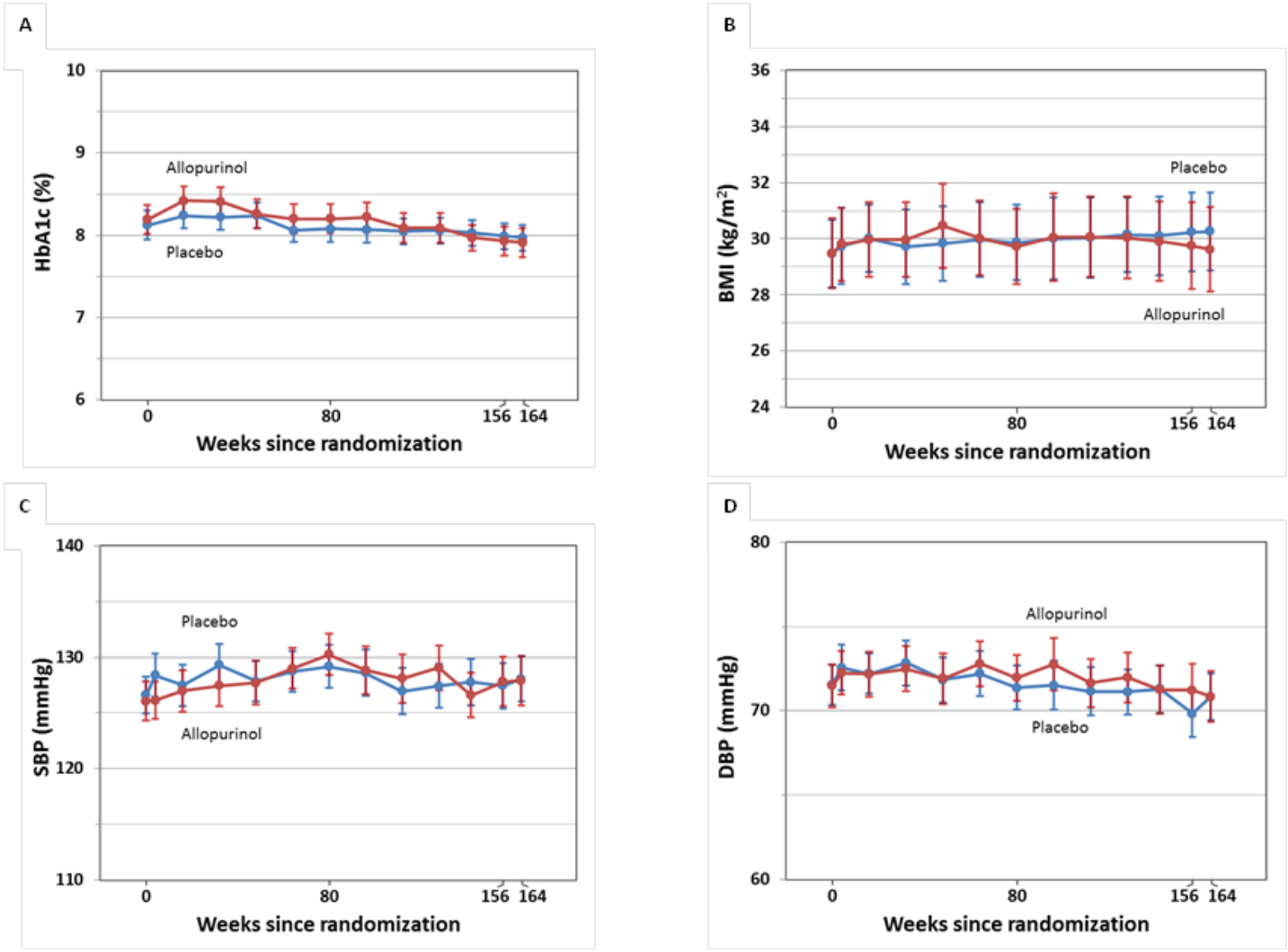

Table S1. Inclusion and Exclusion Criteria for the PERL Study (from Afkarian et al.)[6]

Inclusion criteria
• Male or female T1D patients.

• T1D continuously treated with insulin within one year from diagnosis. If the onset was after age 35, the presence of one or more of the following was also required:
  • documentation of the presence of circulating type 1 diabetes (T1D)-associated autoantibodies at diagnosis or at any other time
  • history of hospitalization for DKA
  • plasma C-peptide below the limit of detection with standard assay (with concurrent blood glucose >100 mg/dl)

• Duration of T1D ≥ 8 years.
• Age 18-70 years.
• History or presence of microalbuminuria or moderate macroalbuminuria, or evidence of declining kidney function regardless of history or presence of albuminuria and/or RAS Blocker (RASB) treatment. Micro- or moderate macroalbuminuria was defined as at least two out of three consecutive urinary albumin excretion rates [AERs] or albumin creatinine ratios [ACRs] taken at any time during the two years before screening or at screening in the 30-5000 mg/24 hr (20-3333 μg/min) or 30-5000 mg/g range, respectively, if not on RASB agents, or in the 18-5000 mg/24 hr (12-3333 μg/min) or 18-5000 mg/g range, respectively, if on RASB); Evidence of declining kidney function was defined as an eGFR (CKD-EPI) decline ≥3.0 ml/min/1.73m^2/year, estimated from the slope derived from all the available serum creatinine measurements (including the one at screening assessment) from the previous 3 years. If at least 3 serum creatinine measures were not available in the previous 3 years, then the slope could be derived from creatinine values from the previous 5 years.
• Estimated GFR (eGFR) based on serum creatinine between 40 and 99.9 ml/min/1.73 m^2 at screening. The upper and the lower limits was decreased by 1 ml/min/1.73 m^2 for each year over age 60 (with a lower limit of 35 ml/min/1.73m^2) and by 10 ml/min/1.73 m^2 for strict vegans.
• Serum uric acid ≥4.5 mg/dL at screening
• Valid baseline (Visit 4) iGFR measurement.
• OR Being an active participant in the PERL Pilot Study.
Exclusion criteria
• History of gout or xanthinuria or other indications for urate lowering therapy such as cancer chemotherapy.
• Recurrent renal calculi.
• Use of urate-lowering agents within 2 months before screening.
• Current use of azathioprine, 6-mercaptopurine, didanosine, warfarin, tamoxifen, amoxicillin/ampicillin, or other drugs interacting with allopurinol.
• Known allergy to xanthine-oxidase inhibitors or iodine containing substances.
• HLA B*58:01 positivity (tested before randomization).
• Renal transplant
• Non-diabetic kidney disease.
• SBP>160 or DBP >100 mmHg at screening or SBP>150 or DBP>95 mmHg at the end of the run-in period.
• Cancer treatment (excluding non-melanoma skin cancer treated by excision) within two

years before screening.
• History of clinically significant hepatic disease including hepatitis B or C and/or persistently elevated serum liver enzymes at screening and/or history of HBV/HCV positivity.
• History of acquired immune deficiency syndrome or human immunodeficiency virus (HIV) infection.
• Hemoglobin concentration at screening <11 g/dL (males), <10 g/dL (females).
• Platelet count at screening <100,000/mm^3.
• History of alcohol or drug abuse in the past 6 months.
• Blood donation in the 3 months before screening.
• Breastfeeding or pregnancy or unwillingness to be on contraception throughout the trial.
• Poor mental function or any other reason to expect patient difficulty in complying with the requirements of the study.
• Serious pre-existing medical problems other than diabetes, e.g. congestive heart failure, pulmonary insufficiency.

Table S2. Baseline Characteristics of Study Participants According to Treatment Arm.

Characteristics*	Placebo	Allopurinol	Total
N	263	267	530
Male, n (%)	168 (63.9)	183 (68.5)	351(66.2)
Age (years)	51.8 ± 10.6	50.4 ± 11.2	51.1 ± 10.9
Age at diabetes diagnosis (years)	17.0 ± 11.2	17.1± 11.4	17.0 ± 11.3
Diabetes duration (years)	35.3 ± 12.5	33.8 ± 12.2	34.6 ± 12.3
Race, n (%)			
White	216 (82.1)	230 (86.1)	446 (84.2)
Black	30 (11.4)	28 (10.5)	58 (10.9)
Asian	5 (1.9)	1 (0.4)	6 (1.1)
Other†	12 (4.6)	8 (3.0)	20 (3.8)
Ethnicity, n (%)			
Non-Hispanic or Non-Latino	254 (96.6)	250 (93.6)	504 (95.1)
Hispanic or Latino	7 (2.7)	16 (6.0)	23 (4.3)
Unknown/Undisclosed	2 (0.8)	1 (0.4)	3 (0.6)
Kidney phenotype, n (%)§			
Albuminuric DKD	206 (78.3)	212 (79.4)	418 (78.9)
Normoalbuminuria with declining kidney function	46 (17.5)	47 (17.6)	93 (17.5)
Indeterminate	4 (1.5)	3 (1.1)	7 (1.3)
Missing	7 (2.7)	5 (1.9)	12 (2.3)
BMI (kg/m^2)¶	29.5 ± 5.9	29.5 ± 6.1	29.5 ± 6.0
HbA1c (%)¶	8.2 ± 1.3	8.2 ± 1.3	8.2 ± 1.3
Serum uric acid (mg/dl)#	6.1 ± 1.5	6.1 ± 1.5	6.1 ± 1.5
Blood pressure (mmHg)#			
Systolic	126.3 ± 13.6	125.6 ± 14.7	126.0 ± 14.2
Diastolic	71.3 ± 10.0	71.2 ± 10.4	71.2 ± 10.2
iGFR (ml per min per 1.73 m^2)¶#	67.3 ± 16.7	68.7 ± 17.1	68.0 ± 16.9
eGFR (ml per min per1.73 m^2)#	74.0 ± 19.4	75.4 ± 18.7	74.7 ± 19.1
Urinary AER (μg per min) ¶^			
Median (IQR)	43.0 (9.0, 198.0)	41.1 (7.7, 216.0)	41.6 (8.5, 207.5)
<20 μg per min, n (%)	92 (35.0)	97 (36.3)	189 (35.7)
20-199 μg per min, n (%)	106 (40.3)	97 (36.3)	203 (38.3)
≥200 μg per min, n (%)	63 (24.0)	73 (27.3)	136 (25.7)
Hypertension, n (%)	241 (91.6)	250 (93.6)	491 (92.6)
Prior self-reported CVD, n (%)¶	54 (21.5)	49 (19.4)	103 (20.5)
Self-reported retinopathy, n (%)¶	163 (64.9)	175 (69.4)	338 (67.2)
Smoking, n (%)			
Current	31 (11.8)	27 (10.1)	58 (10.9)
Past	80 (30.4)	70 (26.2)	150 (28.3)
Never	152 (57.8)	170 (63.7)	322 (60.8)

RASI use, n (%)			
Full dose	174 (66.2)	201 (75.3)	375 (70.8)
Reduced dose	56 (21.3)	46 (17.2)	102 (19.3)
Contraindicated/not indicated	29 (11.0)	19 (7.1)	48 (9.1)
None	4 (1.5)	1 (0.4)	5 (0.9)
HMG-CoA inhibitors, n (%)¶	115 (47.1)	100 (43.9)	215 (45.5)

Abbreviations: GFR = glomerular filtration rate, DKD = diabetic kidney disease, CVD = cardiovascular disease, RASI = renin-angiotensin system inhibitors, hydroxymethylglutaryl-coenzyme A = HMG-CoA, BMI = body mass index, HbA1c = glycated hemoglobin, iGFR = iohexol-GFR, eGFR = serum creatinine based estimated GFR, AER = albumin excretion rate
*Except where noted otherwise, data are mean ± SD for continuous variables and counts (%) for categorical variables.
†Combination of American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander, multi-race, unknown or unreported.
§Albuminuric DKD was defined as presence of albuminuria in the two years before enrollment in the study or during the run-in period; normoalbuminuria with declining kidney function was defined as GFR decline ≥3 ml per min per 1.73 m^2per year) in the previous 3 to 5 years without presence of albuminuria; the "Indeterminate" group includes those participants who could not unequivocally classified based on available data as having albuminuric DKD or normoalbuminuria with declining kidney function; the "Missing" group include 12 participants who, in a retrospective review, did not qualify by albuminuria or GFR slope criteria. Additional details on the definition of these groups can be found in Afkarian et al[6].
¶Data missing for 27 participants for prior self-reported CVD, 27 for self-reported diabetic retinopathy, 58 for HMC-CoA reductase inhibitor use, 5 for BMI, 2 for HbA1c and urine AER, and 1 participant for iGFR.
#Obtained during visit 4.
^Geometric mean of AER values at Visits 3 and 4.

Table S3. Participants Excluded from Per-Protocol Analyses by Preset Criteria.

Criteria	Placebo (N=263)	Allopurinol (N=267)	Total (N=530)
Average weighted drug exposure <80% over all visits	76 (28.9%)	78 (29.2%)	154 (29.1%)
Ineligible participants	11 (4.2%)	6 (2.2%)	17 (3.2%)
Participants taking prohibited medications for >6 months during the 3 year treatment period†	3 (1.1%)	5 (1.9%)	8 (1.5%)
Total	88*	84*	172*

*Totals are less than the sums of participants meeting each criterion as 7 participants (5 in the allopurinol group and 2 in the placebo group) met more than one criterion.
†Prohibited medications included urate-lowering agents and drugs with known interactions with allopurinol.

Table S4. SAEs by Treatment Group Regardless of Relatedness to Intervention (ITT Analysis Set)

	Placebo (N=263)	Allopurinol (N=267)	Total (N=530)
# of SAE's	183	171	354
# of participants with SAE's	82	93	175
SAE's per subject	0.70	0.64	0.67
% of participants with SAE's	31.2	34.8	33.0
P-value*			0.58

*P value from Fisher's exact test comparing frequencies of participants with SAEs by treatment group

Table S5. SAEs by Body System (ITT Analysis Set).

BODY SYSTEM	Placebo (N=263)	Allopurinol (N=267)	Total (N=530)
Infections and infestations	36 (19.7%)	27 (15.8%)	63 (17.8%)
Metabolism and nutrition disorders	35 (19.1%)	25 (14.6%)	60 (16.9%)
Cardiac disorders	23 (12.6%)	32 (18.7%)	55 (15.5%)
Gastrointestinal disorders	13 (7.1%)	18 (10.5%)	31 (8.8%)
Renal and urinary disorders	14 (7.6%)	6 (3.5%)	20 (5.6%)
Injury, poisoning and procedural complications	9 (4.9%)	10 (5.8%)	19 (5.4%)
General disorders and administration site conditions	4 (2.2%)	13 (7.6%)	17 (4.8%)
Nervous system disorders	11 (6.0%)	5 (2.9%)	16 (4.5%)
Surgical and medical procedures	6 (3.3%)	9 (5.3%)	15 (4.2%)
Vascular disorders	8 (4.4%)	3 (1.7%)	11 (3.1%)
Musculoskeletal and connective tissue disorders	7 (3.8%)	3 (1.7%)	10 (2.8%)
Respiratory, thoracic and mediastinal disorders	5 (2.7%)	4 (2.3%)	9 (2.5%)
Pregnancy, puerperium and perinatal conditions	1 (0.6%)	6 (3.5%)	7 (2.0%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	3 (1.6%)	3 (1.7%)	6 (1.7%)
Skin and subcutaneous tissue disorders	2 (1.1%)	3 (1.7%)	5 (1.4%)
Psychiatric disorders	2 (1.1%)	1 (0.6%)	3 (0.8%)
Blood and lymphatic system disorders	1 (0.5%)	1 (0.6%)	2 (0.6%)
Investigations	2 (1.1%)	0	2 (0.6%)
Endocrine disorders	0	1 (0.6%)	1 (0.3%)
Hepatobiliary disorders	0	1 (0.6%)	1 (0.3%)
Reproductive system and breast disorders	1 (0.5%)	0	1 (0.3%)
Total	183 (100%)	171 (100%)	354 (100%)

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