Supplemental Figure Legends

Supplemental Figure 1. Effect of non-calcium-based phosphate binders on change in serum phosphate

Forest plot showing the effect of non-calcium-based phosphate binders compared to placebo or no study treatment on serum phosphate (mg/dL) at last measurement

Supplemental Figure 2. Effect of non-calcium-based phosphate binders on change in urinary phosphate

Forest plot showing the effect of non-calcium-based phosphate binders compared to placebo or no study treatment on urinary phosphate at last measurement

(Units for urinary phosphate: * mg/day; # mmol/L; & mmol/day; % 24hr phosphate:creatinine mg/g; \$ spot urine phosphate:creatinine ratio mg/mg)

Supplemental Figure 3a. Effect of non-calcium phosphate binders on change in serum calcium

Forest plot showing the effect of non-calcium phosphate binders compared to placebo on serum calcium (mg/dL) at last measurement

Supplemental Figure 3b. Effect of non-calcium-based phosphate binders on change in serum calcium

Forest plot showing the effect of non-calcium-based phosphate binders compared to placebo or no study treatment on serum calcium (mg/dL) at last measurement

Supplemental Figure 4a. Effect of non-calcium phosphate binders on change in kidney function (estimated glomerular filtration rate)

Forest plot showing the effect of non-calcium phosphate binders compared to placebo on eGFR (ml/min/1.73²) at last measurement

Supplemental Figure 4b. Effect of non-calcium-based phosphate binders on change in kidney function (estimated glomerular filtration rate)

Forest plot showing the effect of non-calcium-based phosphate binders compared to placebo or no study treatment on eGFR (ml/min/1.73²) at last measurement

Supplemental Figure 5. Effect of non-calcium-based phosphate binders on change in parathyroid hormone (PTH)

Forest plot showing the effect of non-calcium-based phosphate binders compared to placebo or no study treatment on PTH (pg/mL) at last measurement

Supplemental Figure 6a. Effect of non-calcium-based phosphate binders on change in cterminal fibroblast growth factor-23 (cFGF23)

Forest plot showing the effect of non-calcium-based phosphate binders compared to placebo or no study treatment on cFGF23 (RU/mL) at last measurement

Supplemental Figure 6b. Effect of non-calcium-based phosphate binders on change in intact fibroblast growth factor-23 (iFGF23)

Forest plot showing the effect of non-calcium-based phosphate binders compared to placebo or no study treatment on iFGF23 (pg/mL) at last measurement

Supplemental Figure 7. Effect of non-calcium-based phosphate binders on change in pulse wave velocity (PWV)

Forest plot showing the effect of non-calcium-based phosphate binders compared to placebo or no study treatment on PWV (m/s) at last measurement

Supplemental Figure 8. Effect of non-calcium-based phosphate binders on change in vascular calcification

Forest plot showing the effect of non-calcium-based phosphate binders compared to placebo or no study treatment on vascular calcification scores at last measurement

Supplemental Figure 9. Effect of non-calcium-based phosphate binders on mortalityForest plot showing the effect of non-calcium-based phosphate binders compared to placebo or no study treatment on mortality

Supplemental Figure 10. Effect of non-calcium-based phosphate binders on cardiovascular events

Forest plot showing the effect of non-calcium-based phosphate binders compared to placebo or no study treatment on cardiovascular events

Supplemental Figure 11a. Effect of non-calcium-based phosphate binders on nausea

Forest plot showing the effect of non-calcium-based phosphate binders compared to placebo
on nausea

Supplemental Figure 11b. Effect of non-calcium-based phosphate binders on nauseaForest plot showing the effect of non-calcium-based phosphate binders compared to placebo or no study treatment on nausea

Supplemental Figure 12. Effect of non-calcium-based phosphate binders on constipation

Forest plot showing the effect of non-calcium-based phosphate binders compared to placebo or no study treatment on constipation

Supplemental Figure 13a. Effect of non-calcium-based phosphate binders on diarrheaForest plot showing the effect of non-calcium-based phosphate binders compared to placebo on diarrhea

Supplemental Figure 13b. Effect of non-calcium-based phosphate binders on diarrheaForest plot showing the effect of non-calcium-based phosphate binders compared to placebo or no study treatment on diarrhea

Supplemental Figure 14. Effect of non-calcium phosphate binders on cessation of study medication

Forest plot showing the effect of non-calcium phosphate binders compared to placebo on cessation of study medication during the trial

Supplemental Tables

Supplemental Table 1: Search Strategy

- 1. (non calcium adj3 phosphate binder*).mp.
- 2. (phosphate binder* not calcium).mp.
- 3. 1 or 2
- 4. phosphate binder*.mp.
- 5. 4 not 3
- 6. lanthanum carbonate.mp.
- 7. Lanthanum/
- 8. sevelamer hydrochloride.mp. or Sevelamer/
 - 9. ((calcium adj2 magnesium) and binder*).mp.
- 10. bixalomer.mp.
- 11. colestilan.mp.
- 12. (iron and binder*).mp.
- 13. sucroferric oxyhydroxide.mp.
- 14. ferric citrate.mp.
- 15. ((aluminium or aluminum) and binder*).mp.
- 16. nicotinamide.mp. or Niacinamide/
- 17. phosphate.mp.
- 18. 16 and 17
- 19. 1 or 2 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 18
- 20. 4 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 18
- 21. exp renal insufficiency, chronic/ or kidney failure, chronic/
- 22. chronic kidney disease.mp.
- 23. chronic renal failure.mp.
- 24. 21 or 22 or 23
- 25. renal replacement therapy/ or exp renal dialysis/ or hemodiafiltration/ or hemodialysis, home/ or peritoneal dialysis/ or kidney transplantation/
- 26. renal dialysis.mp.
- 27. Renal Dialysis/
- 28. renal transplant*.mp.
- 29. renal allograft.mp.
- 30. exp Dialysis/ or dialysis.mp.
- 31. (hemodialysis or haemodialysis).mp.
- 32. 25 or 26 or 27 or 28 or 29 or 30 or 31
- 33, 20 and 24
- 34. 33 not 32

<u>Supplemental Table 2:</u> GRADE Summary of Evidence for non-calcium-based phosphate binders vs placebo

Number of studies (and participants)	Limitations (Risk of Bias)	Indirectness of patients, intervention and comparator	Inconsistency	Imprecision	Other considerations	Quality of evidence
Serum phosphate (fo	ollow-up 3-24 mon	ths)				
12 studies	Serious	No serious	Serious	No serious	Industry funded trials	⊕⊕00
(1280 participants)	limitations	indirectness	inconsistency	imprecision	-	Low
Urinary phosphate e	excretion (follow-u	p 3-24 months)				
8 studies	Serious	No serious	Serious	No serious	Industry funded trials	⊕⊕00
(702 participants)	limitations	indirectness	inconsistency	imprecision		Low
Serum calcium (foll	ow-up 3-24 month	s)				
11 studies	Serious	No serious	Very serious	No serious	Industry funded trials	⊕000
(1257 participants)	limitations	indirectness	inconsistency	imprecision		Very low
Serum PTH (follow-	up 3-24 months)					
10 trials	Serious	No serious	Very serious	No serious	Industry funded trials	⊕⊕00
(1080 participants)	limitations	indirectness	inconsistency	imprecision		Low
Serum intact FGF2.	3 (follow-up 3-24 i	nonths)				
8 trials	Serious	No serious	Very serious	Serious	Small study bias	⊕000
(937 participants)	limitations	indirectness	inconsistency	imprecision	Industry funded trials	Very low
Serum c-terminal F	GF23 (follow-up 3	-24 months)				
6 trials	Serious	No serious	Very serious	Serious	Industry funded trials	⊕000
(694 participants)	limitations	indirectness	inconsistency	imprecision		Very low
eGFR (follow-up 3-2	24 months)					
9 trials	Serious	No serious	Serious	No serious	Industry funded trials	$\oplus \oplus OO$
(930 participants)	limitations	indirectness	inconsistency	imprecision	-	Low
Mortality (3-24 mon	ths)					

13 trials	Serious	No serious	Very serious	Serious	Industry funded trials	⊕000			
(1479 participants)	limitations	indirectness	inconsistency	imprecision		Very low			
Cardiovascular even	nts (3-24 months)								
7 trials	Serious	No serious	Serious	Serious	Industry funded trials	⊕000			
(873 participants)	limitations	indirectness	inconsistency	imprecision		Very low			
Pulse wave velocity (10-24months)									
3 trials	Very serious	No serious	Very serious	Serious	Industry funded trials	⊕000			
(333 participants)	limitations	indirectness	inconsistency	imprecision		Very low			
Vascular Calcificati	ion (9-24 months)								
3 trials	Very serious	No serious	Very serious	Serious	Industry funded trials	⊕000			
(183 participants)	limitations	indirectness	inconsistency	imprecision	-	Very low			
Cessation of medica	tions (3-24 month	s)							
10 trials	Serious	No serious	Serious	No serious	Industry funded trials	$\oplus \oplus oo$			
(1086 participants)	limitations	indirectness	inconsistency	imprecision		Low			
Nausea (3-24 month	as)								
9 trials	Serious	No serious	No serious	No serious	Industry funded trials	$\oplus \oplus \oplus O$			
(1244 participants)	limitations	indirectness	inconsistency	imprecision	-	Moderate			
Diarrhea (3-12 mon	ths)				·				
8 trials	Serious	No serious	Serious	No serious	Industry funded trials	$\oplus \oplus OO$			
(962 participants)	limitations	indirectness	inconsistency	imprecision		Low			
Constipation (3-12 n	nonths)								
8 trials	Serious	No serious	Serious	No serious	Industry funded trials	$\oplus \oplus OO$			
(900 participants)	limitations	indirectness	inconsistency	imprecision		Low			

Abbreviations: eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone

<u>Supplemental Table 3:</u> Summary of GRADE findings – Non-calcium-based phosphate binders compared to combined placebo or no study medication

Outcomes	Illustrative Comparative Outcomes		Relative effect (95% confidence interval)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Effect non- calcium-based phosphate binders	Risk with placebo or no study treatment*				
Serum phosphate (mg/dL) (3-24 months)	The measure of mean serum phosphate was 0.29 mg/dL lower than the placebo group	The mean serum phosphate was 4.23 mg/dL	-0.49 – -0.10	1596 (15)	⊕⊕OO Due to risk of bias and inconsistency	Considerable heterogeneity (I ² = 85%)
Urinary phosphate excretion (SMD) (3-24 months)	The measure of mean urinary phosphate excretion was 0.61 standard units lower than with placebo	The mean urinary phosphate was 423.1 standard units	-0.840.38	964 (10)	⊕⊕OO Due to risk of bias and inconsistency	Different units of urinary phosphate excretion including ratios added to inconsistency of results
Serum PTH (pg/dL) (3-24 months)	The measure of mean serum PTH was unchanged in comparison to placebo	The mean serum PTH was 125.6 pg/dL	-15.47 – 10.55	1319 (14)	⊕⊕OO Due to risk of bias and inconsistency of results	Some inconsistency in results regarding effect on PTH
Pulse wave velocity	The PWV was unchanged	The mean PWV was 10.2 m/s	-0.46 – 1.05	507 (5)	⊕OOO Due to risk of bias,	3 studies only able to be analysed, with 2 sets of mean values being identical

(m/s)					imprecision and inconsistency	(likely due to transformation of median to mean for
(10-24 months)					meomoratemey	analysis)
Vascular	There was a	High	0.02 - 0.56	320	⊕000	Statistically significant
calcification	small degree of	background risk of		(5)	Due to risk of	(p<0.01)
(Standard units)	effect on vascular calcification	vascular			bias, imprecision and	Not likely to be of clinical significance.
(9-24 months)	(Hedge's g=0.29)	calcification in CKD depending on			inconsistency	3 studies only able to be analysed.
		stage				
Mortality	There was no	Risk with	-1.41 – 0.97	1942	⊕000	Large confidence intervals
(log OR)	significant difference in	placebo 2/100 person		(17)	Due to risk of bias,	leading to imprecision. Studies often not powered or
(3-24 months)	mortality rate between the two groups (log OR -0.22)	years			imprecision and inconsistency	had long enough follow-up geared to considerations of mortality
Cardiovascular	There was no	Not estimable	-0.58 - 0.88	1072	⊕000	Few events and not powered
events	difference in the			(8)	Due to risk of	for follow-up
(log OR)	risk of cardiovascular				bias, imprecision and	
(3-24 months)	events between				inconsistency	
	non-calcium binders and no study treatment					
	$(\log OR \ 0.15)$					

^{*} Calculations for overall weighted means for serum and urinary phosphate, PTH and PWV – sum of weighted placebo means across studies for each variable.

Supplemental Table 4: GRADE Summary of Evidence for non-calcium phosphate binders vs placebo or no study treatment

Number of studies (and participants)	Limitations (Risk of Bias)	Indirectness of patients, intervention and comparator	Inconsistency	Imprecision	Other considerations	Quality of evidence
Serum phosphate (fe	ollow-up 3-24 moi	nths)	1			
15 studies	Serious	No serious	Serious	No serious	Industry funded trials	$\oplus \oplus OO$
(1596 participants)	limitations	indirectness	inconsistency	imprecision		Low
Urinary phosphate e	excretion (follow-u	up 3-24 months)				
10 studies	Serious	No serious	Serious	No serious	Industry funded trials	⊕⊕00
(964 participants)	limitations	indirectness	inconsistency	imprecision		Low
Serum calcium (foll	ow-up 3-24 month	us)				
13 studies	Serious	No serious	Very serious	No serious	Industry funded trials	⊕000
(1519 participants)	limitations	indirectness	inconsistency	imprecision		Very low
Serum PTH (follow-	up 3-24 months)					
14 trials	Serious	No serious	Very serious	No serious	Industry funded trials	⊕⊕00
(1319 participants)	limitations	indirectness	inconsistency	imprecision		Low
Serum intact FGF2.	3 (follow-up 3-24)	months)				
12 trials	Serious	No serious	Very serious	Serious	Small study bias	⊕000
(1224 participants)	limitations	indirectness	inconsistency	imprecision	Industry funded trials	Very low
Serum c-terminal F	GF23 (follow-up 3	3-24 months)				
7 trials	Serious	No serious	Very serious	Serious	Industry funded trials	⊕000
(854 participants)	limitations	indirectness	inconsistency	imprecision		Very low
eGFR (follow-up 3-2	24 months)					-
12 trials	Serious	No serious	Serious	No serious	Industry funded trials	⊕⊕00
(1191 participants)	limitations	indirectness	inconsistency	imprecision		Low
Mortality (3-24 mon	ths)		•			

17 trials	Serious	No serious	Very serious	Serious	Industry funded trials	⊕000			
(1942 participants)	limitations	indirectness	inconsistency	imprecision		Very low			
Cardiovascular even	ets (3-24 months)					•			
8 trials	Serious	No serious	Serious	Serious	Industry funded trials	⊕000			
(1072 participants)	limitations	indirectness	inconsistency	imprecision		Very low			
Pulse wave velocity (10-24months)									
5 trials	Very serious	No serious	Serious	Serious	Industry funded trials	$\oplus \oplus OO$			
(507 participants)	limitations	indirectness	inconsistency	imprecision		Very low			
Vascular calcification	on (9-24 months)								
5 trials	Very serious	No serious	Serious	Serious	Industry funded trials	⊕000			
(320 participants)	limitations	indirectness	inconsistency	imprecision		Very low			
Cessation of medica	tions (3-24 months	s)							
10 trials	Serious	No serious	Serious	No serious	Industry funded trials	⊕000			
(1086 participants)	limitations	indirectness	inconsistency	imprecision		Very low			
Nausea (3-24 month	es)								
10 trials	Serious	No serious	No serious	No serious	Industry funded trials	$\oplus \oplus \oplus O$			
(1350 participants)	limitations	indirectness	inconsistency	imprecision		Moderate			
Diarrhea (3-12 mon	ths)								
8 trials	Serious	No serious	Serious	No serious	Industry funded trials	$\oplus \oplus oo$			
(962 participants)	limitations	indirectness	inconsistency	imprecision		Low			
Constipation (3-12 n	nonths)								
9 trials	Serious	No serious	Serious	No serious	Industry funded trials	$\oplus \oplus oo$			
(1006 participants)	limitations	indirectness	inconsistency	imprecision		Low			

Abbreviations: eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone

<u>Supplemental Table 5:</u> Summary of GRADE findings – Non-calcium phosphate-lowering therapy compared to placebo

Outcomes	Illustrative Comparative Outcomes	Comparative		Number of participants (studies)	Quality of evidence (GRADE)	Comments
	Effect of non- calcium phosphate- lowering therapy	Risk with placebo*				
Serum phosphate (mg/dL) (3-24 months)	The measure of mean serum phosphate was 0.3 mg/dL lower than the placebo group	The mean serum phosphate was 4.28 mg/dL	-0.55 – -0.14	1330 (12)	⊕⊕OO Due to risk of bias and inconsistency	Considerable heterogeneity (I ² = 85%)
Urinary phosphate excretion (SMD) (3-24 months)	The measure of mean urinary phosphate excretion was 0.55 standard units lower.	The mean urinary phosphate was 432.5 standard units	-0.83 – -0.27	753 (8)	⊕⊕OO Due to risk of bias and inconsistency	Different units of urinary phosphate excretion including ratios added to inconsistency of results (I ² =68.3%)
Serum PTH (pg/dL) (3-24 months)	The measure of mean serum PTH was unchanged	The mean serum PTH was 130.5 pg/dL	-20.21 – 7.16	1131 (11)	⊕OOO Due to risk of bias and inconsistency of results	Some inconsistency in results regarding effect on PTH (I ² =69% with large confidence intervals)
Vascular calcification	There was a suggestion of a moderate	High background risk of	0.17 – 0.77	320 (3)	⊕OOO Due to risk of bias,	Two studies only with a small number of participants

vascular calcification with phosphate-lowering medication (Hcdge's g=0.47)	(Standard units)	increase in	vascular			imprecision and	
CKD depending on stage CKD CAMD Due to some risk of bias, imprecision and inconsistency Due to risk of bias, imprecision and inconsistency depending on stage CKD Due to risk of bias, imprecision and inconsistency depending on stage CKD Due to risk of bias, imprecision and inconsistency depending on stage CKD Due to risk of bias, imprecision and inconsistency depending on stage CKD CKD Due to risk of bias, imprecision and inconsistency depending on stage CKD Due to risk of bias, imprecision and inconsistency depending on stage CKD Due to risk of bias, imprecision and inconsistency depending on stage CKD Due to risk of bias, imprecision and inconsistency depending on stage CKD Due to risk of bias, imprecision and inconsistency depending on stage CKD Due to risk of bias, imprecision and inconsistency depending on stage CKD Due to risk of bias, imprecision and inconsistency depending on stage CKD Due to risk of bias, imprecision and inconsistency depending on stage CKD Due to risk of bias, imprecision and inconsistency depending on stage CKD Due to risk of bias, imprecision and inconsistency depending on stage CKD Due to risk of bias, imprecision and inconsistency depending on stage CKD Due to ris	(Statiania attis)					_	
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pulse wave velocity with phosphate lowering medication Mortality (10-24 months) Mortality (10-24 months) Mortality (10-24 months) There was no significant difference in word groups (log OR - 0.56) Cardiovascular event risk (3-24 months) pulse wave velocity with phosphate lowering medication Risk with placebo (8) 1-1.99 – 0.87 1530 (8) Due to risk of bias, imprecision and inconsistency Risk with placebo (8) Due to risk of bias, Studies often not powered or had long enough follow-up geared to considerations of mortality Studies often not powered or had long enough follow-up geared to considerations of mortality There was no significant difference in the cardiovascular event risk There was no significant difference in the cardiovascular event risk Not estimable inconsistency				-0.46 – 1.05		•	Three studies only
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Iowering medication	(m/s)	velocity with	was 10.4m/s			imprecision and	
Iowering medication There was no significant difference in groups (log OR -0.56) Cardiovascular events (3-24 months) Cardiovascular event risk Cardiovascular	(10-24 months)	phosphate				inconsistency	
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Significant difference in difference in mortality risk between the two groups (log OR -0.56)		medication					
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(3-24 months) mortality risk between the two groups (log OR -0.56) Cardiovascular events (3-24 months) (3-24 months) mortality risk between the two groups (log OR -0.56) Not estimable (7) mortality risk between the two geared to considerations of mortality 873 (7) Due to risk of bias, imprecision and inconsistency imprecision and inconsistency		significant	placebo		(8)	Due to risk of	leading to imprecision.
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(3-24 months) cardiovascular event risk imprecision and inconsistency						bias,	
event risk inconsistency	(3-24 months)					· · · · · · · · · · · · · · · · · · ·	
						_	
between the two							
groups							

 $^{* \} Calculations \ for \ overall \ weighted \ means \ for \ serum \ and \ urinary \ phosphate, \ PTH \ and \ PWV-sum \ of \ weighted \ placebo \ means \ across \ studies \ for \ each \ variable$

Supplemental Table 6: GRADE Summary of Evidence for non-calcium phosphate-lowering therapy vs placebo

Number of studies (and participants)	Limitations (Risk of Bias)	Indirectness of patients, intervention and comparator	Inconsistency	Imprecision	Other considerations	Quality of evidence
Serum phosphate (fe	ollow-up 3-24 moi	nths)	1			
12 studies	Serious	No serious	Serious	No serious	Industry funded trials	$\oplus \oplus OO$
(1330 participants)	limitations	indirectness	inconsistency	imprecision	-	Low
Urinary phosphate e	excretion (follow-u	up 3-24 months)				
8 studies	Serious	No serious	Serious	No serious	Industry funded trials	$\oplus \oplus OO$
(753 participants)	limitations	indirectness	inconsistency	imprecision		Low
Serum calcium (foll	ow-up 3-24 month	us)	•			
11 studies	Serious	No serious	Very serious	No serious	Industry funded trials	⊕000
(1308 participants)	limitations	indirectness	inconsistency	imprecision		Very low
Serum PTH (follow-	up 3-24 months)					
11 trials	Serious	No serious	Very serious	No serious	Industry funded trials	⊕⊕00
(1131 participants)	limitations	indirectness	inconsistency	imprecision		Low
Serum intact FGF23	3 (follow-up 3-24)	months)				
9 trials	Serious	No serious	Very serious	Serious	Small study bias	⊕000
(988 participants)	limitations	indirectness	inconsistency	imprecision	Industry funded trials	Very low
Serum c-terminal F	GF23 (follow-up 3	3-24 months)				
6 trials	Serious	No serious	Very serious	Serious	Industry funded trials	⊕000
(694 participants)	limitations	indirectness	inconsistency	imprecision		Very low
eGFR (follow-up 3-2	24 months)					
9 trials	Serious	No serious	Serious	No serious	Industry funded trials	⊕⊕00
(981 participants)	limitations	indirectness	inconsistency	imprecision		Low
Mortality (3-24 mon	ths)					

13 trials	Serious	No serious	Very serious	Serious	Industry funded trials	⊕000
(1530 participants)	limitations	indirectness	inconsistency	imprecision		Very low
Cardiovascular even	nts (3-24 months)					
7 trials	Serious	No serious	Serious	Serious	Industry funded trials	⊕000
(873 participants)	limitations	indirectness	inconsistency	imprecision		Very low
Pulse wave velocity	(10-24months)					
3 trials	Very serious	No serious	Serious	Serious	Industry funded trials	⊕000
(333 participants)	limitations	indirectness	inconsistency	imprecision		Very low
Vascular calcification	on (9-24 months)					
3 trials	Very serious	No serious	Very serious	Serious	Industry funded trials	⊕000
(320 participants)	limitations	indirectness	inconsistency	imprecision		Very low
Cessation of medica	tions (3-24 month	s)				•
10 trials	Serious	No serious	Serious	No serious	Industry funded trials	$\oplus \oplus OO$
(1086 participants)	limitations	indirectness	inconsistency	imprecision		Low
Nausea (3-24 month	as)					
9 trials	Serious	No serious	No serious	No serious	Industry funded trials	$\oplus \oplus \oplus O$
(1295 participants)	limitations	indirectness	inconsistency	imprecision		Moderate
Diarrhea						
8 trials	Serious	No serious	Very serious	No serious	Industry funded trials	⊕000
(936 participants)	limitations	indirectness	inconsistency	imprecision		Very low
Constipation						
8 trials	Serious	No serious	Very serious	No serious	Industry funded trials	⊕000
(900 participants)	limitations	indirectness	inconsistency	imprecision		Very low

Abbreviations: eGFR, estimated glomerular filtration rate; FGF23, fibroblast growth factor 23; PTH, parathyroid hormone

<u>Supplemental Table 7:</u> Summary of GRADE findings – Non-calcium-based phosphate binders compared to calcium-based phosphate binders

Outcomes	Illustrative Comparative		Relative effect (95% confidence	Number of participants	Certainty of evidence	Comments
	Outcomes		interval)	(studies&)	(GRADE)	
	Effect of non- calcium-based phosphate binders	Risk with calcium-based phosphate binders*				
Serum phosphate (mg/dL) (4-36 months)	The measure of mean serum phosphate was not lower with non-calcium phosphate binders	The mean serum phosphate was 4.47 mg/dL	-0.35 – 0.22	436 (5)	⊕OOO Due to high risk of bias and very serious inconsistency	Considerable heterogeneity (I ² =79%)
Urinary phosphate excretion (SMD) (4-24 months)	The measure of mean urinary phosphate excretion was not lower with non-calcium phosphate binders	The mean urinary phosphate was 380.8 standard units	-3.171.00	152 (3)	⊕OOO Due to high risk of bias and very serious inconsistency	Different units of urinary phosphate excretion including ratios added to inconsistency of results. Considerable heterogeneity (I ² = 97%)
Serum calcium (mg/dL) (4-36 months)	The measure of mean serum calcium was not higher with non-calcium phosphate binders	The mean serum calcium was 9.42 mg/dL	-0.70 – 0.15	436 (5)	⊕OOO Due to high risk of bias and very serious inconsistency	Very serious inconsistency in results regarding effect on non-calcium-based phosphate binders on serum calcium. Considerable heterogeneity (I ² = 96%)

Serum PTH (pg/dL) (4-36 months)	The measure of mean serum PTH was unchanged	The mean serum PTH was 212.2 pg/dL	-17.58 – 10.97	1131 (5)	⊕OOO Due to high risk of bias and inconsistency of results	Some inconsistency in results regarding effect on PTH
Mortality (log OR) (4-36 months)	There was no significant difference in mortality rate between non-calcium binders and calcium binders (log OR -0.70)	Risk with placebo 2/100 person years	-1.45 – 0.05	421 (4)	⊕OOO Due to high risk of bias, imprecision and inconsistency	Large confidence intervals, with only one large trial leading to any events being recorded
Vascular calcification (Standard units) (9-24 months)	There was no apparent difference in vascular calcification with non-calcium or calcium phosphate binders (0.05)	High background risk of vascular calcification in CKD depending on stage	-0.43 – 0.53	120 (2)	⊕OOO Due to risk of bias, imprecision and inconsistency	Two studies only with a small number of participants

[#] The majority for studies had risk of bias for allocation concealment and performance bias & The calcium-based binder arm of Block (2012) included

^{*} Calculations for overall weighted means for serum and urinary phosphate, calcium, PTH and PWV – sum of weighted placebo means across studies for each variable

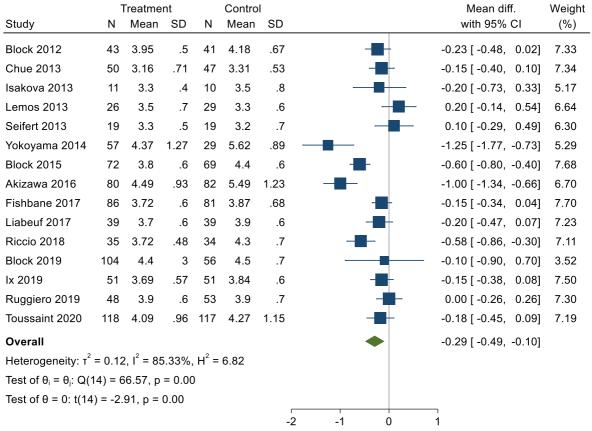
Supplemental Table 8: GRADE Summary of Evidence for non-calcium-based phosphate binders vs calcium-based phosphate binders

Number of studies (and participants)	Limitations (Risk of Bias)	Indirectness of patients, intervention and comparator	Inconsistency	Imprecision	Other considerations	Quality of evidence
Serum phosphate (fol	low-up 4-36 mon	eths)				
5 studies (436 participants)	Very serious limitations	No serious indirectness	Very serious inconsistency	No serious imprecision	Industry funded trials	⊕OOO Very low
Urinary phosphate ex	cretion (follow-u		, ,	1	- 1	
3 studies (152 participants) Serum calcium (followard)	Very serious limitations	No serious indirectness	Very serious inconsistency	No serious imprecision	Industry funded trials	⊕OOO Very low
5 studies (436 participants)	Very serious limitations	No serious indirectness	Very serious inconsistency	No serious imprecision	Industry funded trials	⊕OOO Very low
Serum PTH (follow-u		Lat.	T 7 ·		T 1 (C 1 1 (1 1	0000
5 trials (1131 participants)	Very serious limitations	No serious indirectness	Very serious inconsistency	No serious imprecision	Industry funded trials	⊕OOO Very low
eGFR (follow-up 3-24	4 months)					
3 trials (152 participants) Mortality (4-24 month)	Very serious limitations	No serious indirectness	Serious inconsistency	No serious imprecision	Industry funded trials	⊕OOO Very low
4 trials	Very serious	No serious	Very serious	Serious	Industry funded triels	Φοοο
(421 participants) Vascular calcification	limitations	indirectness	inconsistency	imprecision	Industry funded trials	⊕OOO Very low
2 trials	Very serious	No serious	Serious	Serious	Industry funded trials	⊕000
(120 participants)	limitations	indirectness	inconsistency	imprecision	industry runded trials	Very low

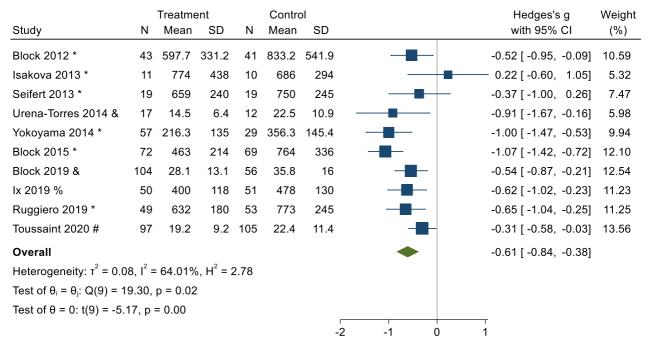
Abbreviations: eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone

Supplemental Figures

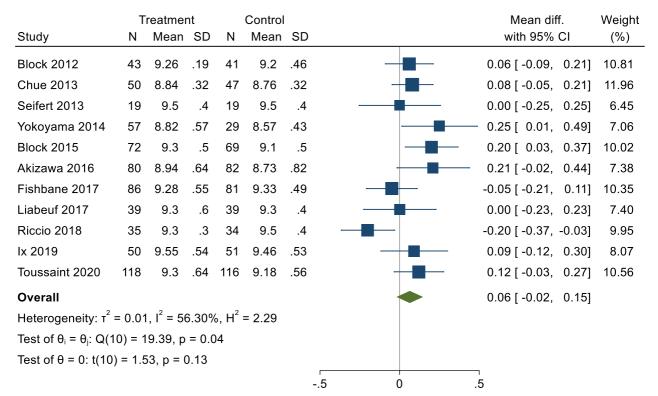
<u>Supplemental Figure 1:</u> Effect of non-calcium-based phosphate binders compared to placebo or no study treatment on serum phosphate.



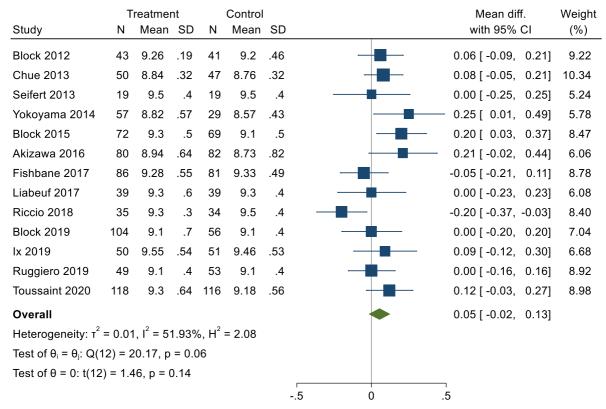
<u>Supplemental Figure 2:</u> Effect of non-calcium phosphate binders compared to placebo or no study treatment on urinary phosphate.



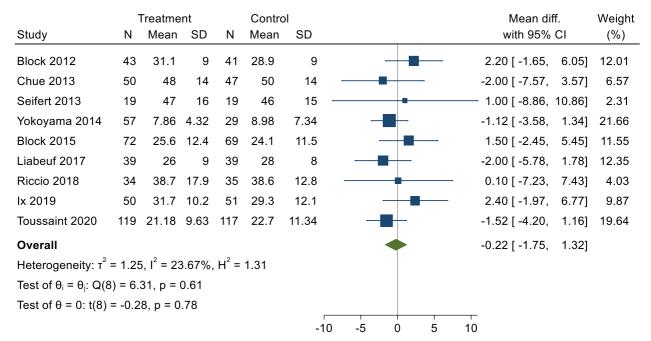
<u>Supplemental Figure 3a:</u> Effect of non-calcium phosphate binder compared to placebo on serum calcium.



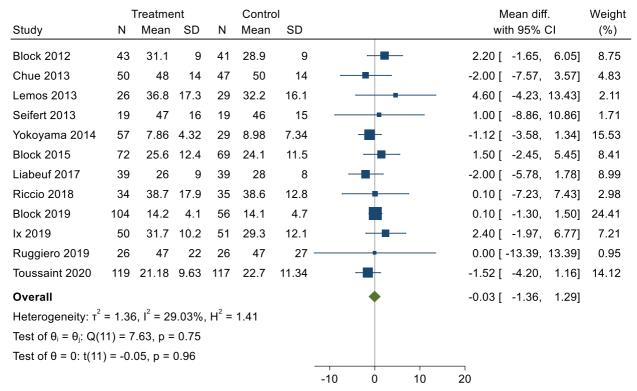
<u>Supplemental Figure 3b:</u> Effect of non-calcium phosphate binders compared to placebo or no study treatment on serum calcium.



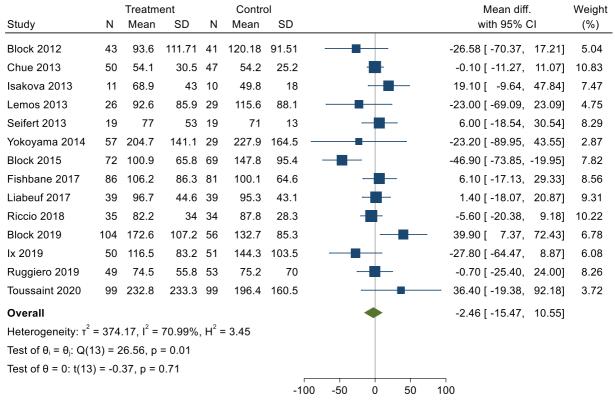
<u>Supplemental Figure 4a:</u> Effect of non-calcium phosphate binders compared to placebo on eGFR.



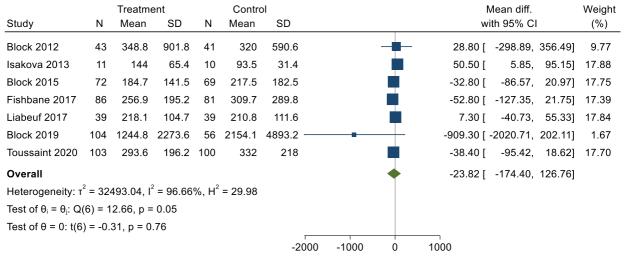
<u>Supplemental Figure 4b:</u> Effect of non-calcium-based phosphate binders compared to placebo or no study treatment on eGFR.



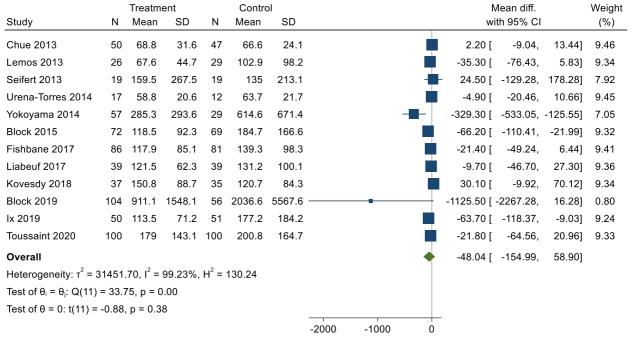
<u>Supplemental Figure 5:</u> Effect of non-calcium-based phosphate binders compared to placebo or no study treatment on PTH.



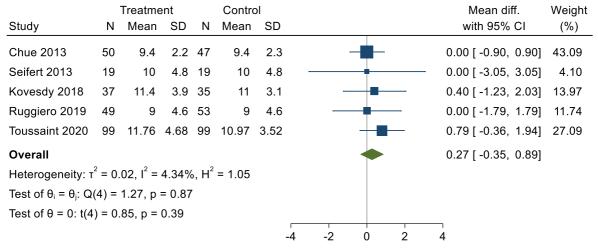
<u>Supplemental Figure 6a:</u> Effect of non-calcium-based phosphate binders compared to placebo or no study treatment on cFGF23.



<u>Supplemental Figure 6b:</u> Effect of non-calcium-based phosphate binders compared to placebo or no study treatment on iFGF23.

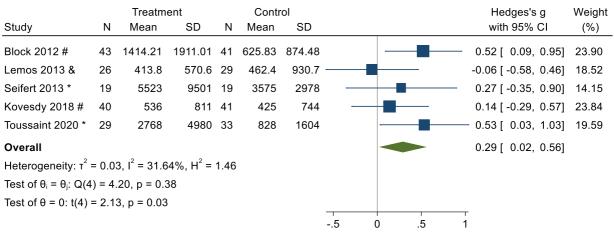


<u>Supplemental Figure 7:</u> Effect of non-calcium-based phosphate binders compared to placebo or no study treatment on PWV.

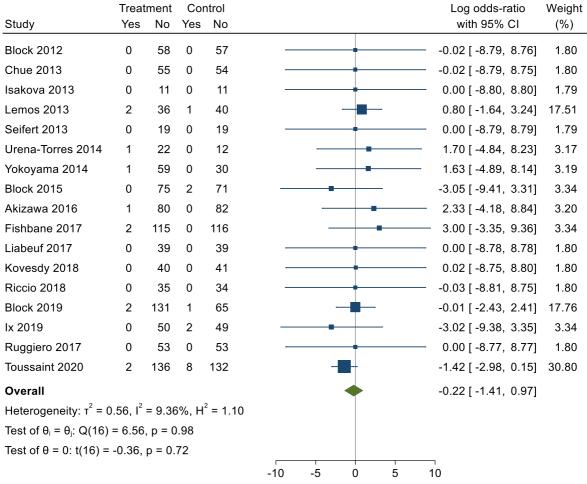


Random-effects Sidik-Jonkman model

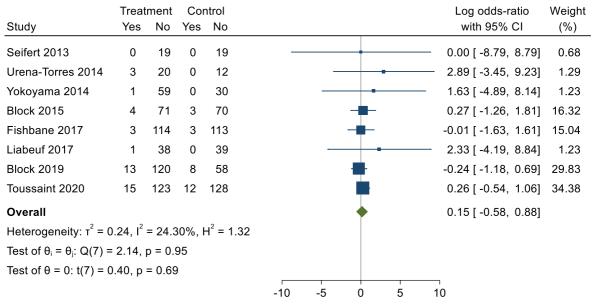
<u>Supplemental Figure 8:</u> Effect of non-calcium-based phosphate binders compared to placebo or no study treatment on vascular calcification.



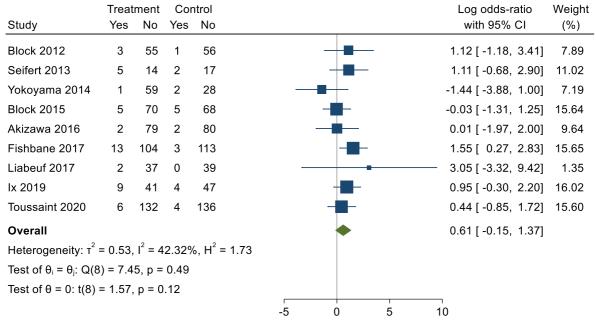
<u>Supplemental Figure 9:</u> Effect of non-calcium-based phosphate binders compared to placebo or no study treatment on mortality.



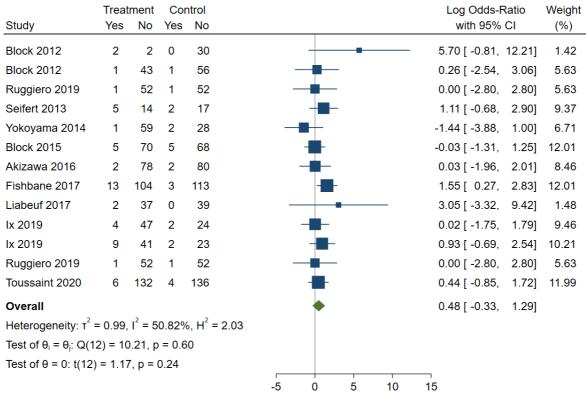
<u>Supplemental Figure 10:</u> Effect of non-calcium-based phosphate binders compared to placebo or no study treatment on cardiovascular events.



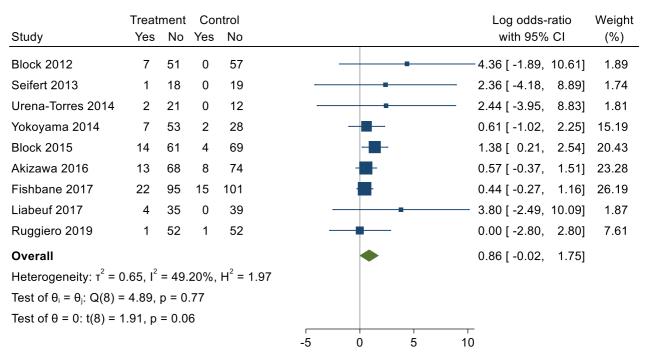
<u>Supplemental Figure 11a:</u> Effect of non-calcium-based phosphate binders compared to placebo on nausea.



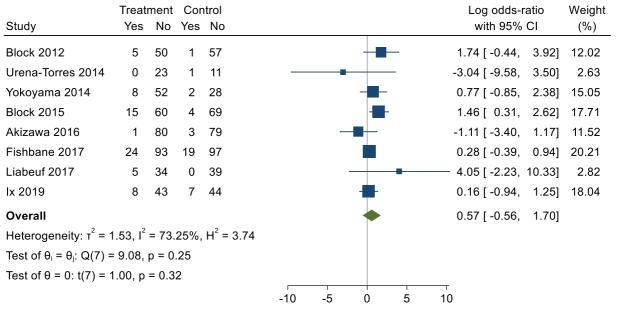
<u>Supplemental Figure 11b:</u> Effect of non-calcium-based phosphate binders compared to placebo or no study treatment on nausea.



<u>Supplemental Figure 12:</u> Effect of non-calcium-based phosphate binders compared to placebo or no study treatment on constipation.

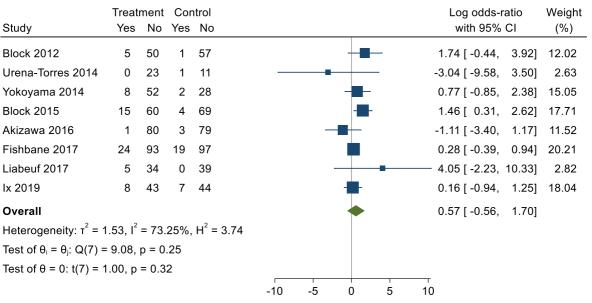


<u>Supplemental Figure 13a:</u> Effect of non-calcium-based phosphate binders compared to placebo on diarrhea.



Random-effects Sidik-Jonkman model

<u>Supplemental Figure 13b:</u> Effect of non-calcium-based phosphate binders compared to placebo or no study treatment on diarrhea.



<u>Supplemental Figure 14:</u> Effect of non-calcium phosphate binders compared to placebo on cessation of study medication.

