Recent advances in CKD-MBD treatment

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Pathogenesis of secondary hyperparathyroidism

- Calcitriol
- CaR
- VDR
- PTH
- Ca²⁺
- Phosphate
- PTH secretion
- PTH synthesis
- Cell proliferation

Vitamin D deficiency and sHPT start to manifest in early stages of CKD.
Hyperphosphatemia starts to manifest sich in stages 4-5 in CKD patients

Phosphate Balance

- **P-Uptake**: 20 mg/kg/day
- **16 mg/kg/day intestinal absorption**
- **Faeces**: 7 mg/kg/day
- **Intestinal fluid**: 3 mg/kg/day
- **Bone**: 3 mg/kg/day
- **Extracellular phosphate pool**: CKD5D
- **Kidney**: 13 mg/kg/day

adapted: Schiavi & Kumar, Kidney Int 2004; 65:1-14
FGF-23

How Fibroblast Growth Factor 23 Works

Shiguang Liu and L. Darryl Quarles
Kidney Institute, University of Kansas Medical Center, Kansas City, Kansas

Biochemical parameters in FGF23 knockout mice

Shimada et al., J Clin Invest 2004; 113:561-8
KLOTHO –
the Greek goddess of fate who spins the thread of life
How FGF-23 works!


**Factors Stimulating FGF23**
- Parathyroid Gland
- FGFR:Klotho
- PTH

**Serum-derived**
- Serum PO$_4^{2-}$
- 1,25 (OH)$_2$D

**Matrix-derived**
- Phex
- DMP1

**Kidney**
- FGFR:Klotho
- PO$_4^{2-}$ absorption
- 1,25(OH)$_2$ Vit D synthesis

**Bone**
- Mineralized Bone
- Osteoid
- Osteoblast
- MEPE-ASARM
- DMP1
- SOST
- Frizzled
- LRP5
“Loss-of-function“ mutation of the *Klotho* gene causes a phenotype of „AGING“

*Klotho* knockout mice develop...

... Calcifying atherosclerosis
... Osteoporosis
... Skin atrophy
... Emphysema
... Infertility

... and die prematurely.

Transgenic *Klotho* overexpression rescues this phenotype.

Kuro-o et al., Nature 390:45-51
FGF-23 knockout mice die prematurely, but can be rescued by correction of either hyperphosphatemia or hypervitaminosis D.
How FGF-23 works!

Aortic calcifications in FGF-23-/ mice fed different diets

Kidney calcifications in FGF-23-/ mice fed different diets

PD = Phosphate-deficient diet
DD = Vitamin D-deficient diet

FGF23 and chronic kidney disease (CKD) stage inversely correlate with each other

Relative fractional phosphate excretion increases with CKD progression

Phosphate binding by sevelamer reproducible lowers FGF23 and PTH levels in hyperphosphatemic uremic rats

Nagano et al., Kidney Int 2006; 69:531-7
Pathogenesis of secondary hyperparathyroidism

Calcitriol

FGF23

Calcium

Phosphate

FGF23

In CKD 5D, FGF23 serum levels correlate as well with phosphate concentrations.
Fibroblast Growth Factor 23 and Mortality among Patients Undergoing Hemodialysis

Orlando M. Gutiérrez, M.D., M.M.Sc., Michael Mannstadt, M.D.,
Tamara Isakova, M.D., Jose Alejandro Rauh-Hain, M.D., Hector Tarnez, M.D.,
Anand Shah, M.D., Kelsey Smith, B.A., Hang Lee, Ph.D.,

Table 2. Laboratory Results and Use or Nonuse of Phosphorus Binders, According to Quartiles of cFGF-23 Level.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>cFGF-23 Quartile 1 (&lt;1090 RU/ml)</th>
<th>cFGF-23 Quartile 2 (1090–1750 RU/ml)</th>
<th>cFGF-23 Quartile 3 (1751–4010 RU/ml)</th>
<th>cFGF-23 Quartile 4 (&gt;4010 RU/ml)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (g/dl)</td>
<td>3.4±0.5</td>
<td>3.3±0.5</td>
<td>3.3±0.6</td>
<td>3.3±0.5</td>
<td>0.13</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>5.3±2.2</td>
<td>5.4±2.2</td>
<td>6.3±2.2</td>
<td>6.6±2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Phosphate (mg/dl)</td>
<td>3.9±1.2</td>
<td>4.1±1.3</td>
<td>4.5±1.6</td>
<td>5.2±2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>8.8±0.8</td>
<td>8.9±0.7</td>
<td>8.8±0.8</td>
<td>9.0±0.8</td>
<td>0.15</td>
</tr>
<tr>
<td>Parathyroid hormone (pg/ml)</td>
<td>180 (99–313)</td>
<td>137 (95–273)</td>
<td>253 (119–377)</td>
<td>234 (145–435)</td>
<td>0.22</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/liter)</td>
<td>82 (64–103)</td>
<td>89 (67–114)</td>
<td>91 (69–114)</td>
<td>100 (77–131)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1,25-Dihydroxyvitamin D (pg/ml)†</td>
<td>9.1±5.2</td>
<td>6.9±6.0</td>
<td>8.4±5.0</td>
<td>7.5±5.8</td>
<td>0.45</td>
</tr>
<tr>
<td>Phosphorus binders (% of patients)</td>
<td>12</td>
<td>8</td>
<td>9</td>
<td>6</td>
<td>0.18</td>
</tr>
</tbody>
</table>
High FGF23 are mortality risk predictors in incident hemodialysis patients.
FGF23 and mortality in CKD 5D: The ArMORR study


Table 3. Levels of cFGF-23 and Associated Risk of Death within Serum Phosphate Quartiles in the Case–Control Sample.

<table>
<thead>
<tr>
<th>Phosphate Level</th>
<th>Median cFGF-23 Level (interquartile range)</th>
<th>P Value</th>
<th>Odds Ratio for Death (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients Who Died (N = 200)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients Who Survived (N = 200)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>reference units per milliliter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All levels</td>
<td>2260 (1196–5296)</td>
<td>1406 (989–2741)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;3.5 mg/dl</td>
<td>1790 (1175–3941)</td>
<td>1148 (927–2169)</td>
<td>0.008</td>
</tr>
<tr>
<td>3.5–4.4 mg/dl</td>
<td>2049 (1109–4865)</td>
<td>1131 (893–1629)</td>
<td>0.003</td>
</tr>
<tr>
<td>4.5–5.5 mg/dl</td>
<td>2207 (1186–5238)</td>
<td>1499 (1044–2262)</td>
<td>0.02</td>
</tr>
<tr>
<td>&gt;5.5 mg/dl</td>
<td>3541 (1871–10,491)</td>
<td>2686 (1527–6210)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Significant associations FGF23 and mortality in serum phosphate levels within the KDOQI target range (<5.5 mg/dl !)
High levels of serum fibroblast growth factor (FGF)-23 are associated with increased mortality in long haemodialysis patients

Guillaume Jean, Jean-Claude Terrat, Thierry Vanel, Jean-Marc Hurot, Christie Lorriaux, Brice Mayor and Charles Chazot

![Graph 1](image1.png)

**Fig. 1.** Regression of phosphataemia against log FGF-23 ($r^2 = 0.11$, $P < 0.001$).

![Graph 2](image2.png)
As nature did not predict dialysis—what we can learn from FGF23 in end-stage renal disease?

Markus Ketteler and Patrick H. Biggar

- High FGF23 despite long dialysis sessions – is initial resorption more important than overall balance?

- Warfarin use was associated with high FGF23 – link between vitamin K-dependent pathways (Osteocalcin/MGP), FGF23 regulation and calcification?

- Influence of active vitamin D treatment on FGF23 levels?
Pathogenesis of secondary hyperparathyroidism


Reduction in glomerular filtration rate
Inadequate dialysis
Nonadherence to dietary restriction or dialysis regimen

Hyperphosphatemia

- Direct vascular injury
  - Vascular calcification
  - Endothelial dysfunction
  - Oxidative stress

- Increased fibroblast growth factor 23
  - Unknown mechanisms

- Inhibition of 1,25-dihydroxy-vitamin D synthesis
  - Decreased cardiac contractility
  - Coronary-artery calcification
  - Myocardial fibrosis
  - Proinflammatory effect

- Increased parathyroid hormone
  - Proinflammatory effect
  - Increased interleukin-6
  - Impaired myocardial energy production
  - Cardiac fibrosis

Increased cardiovascular risk
Management of hyperphosphatemia by phosphate binders

- **Ca-Ac/-Carb (TTG)**
- **Sevelamer (TTG)**
- **Ca-Ac (CARE)***
- **Lanthanum**

*S-Phosphate (mmol/l) vs. weeks*  

K/DOQI Limit

* Treat-to-goal Studie: Chertow GM. KI 2002; ** Hutchison WCN 03. Berlin; *** Qunibi W. et al. KI 2004*
## Available phosphate binders

<table>
<thead>
<tr>
<th>Calcium-based phosphate binders</th>
<th>Calcium-free phosphate binders</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Calciumcarbonate</td>
<td>• Aluminium-HCl / Aluminium-OH</td>
</tr>
<tr>
<td>• Calciumacetate</td>
<td>• Sevelamer-HCl / Sevelamercarbonate</td>
</tr>
<tr>
<td></td>
<td>• Lanthanumcarbonate</td>
</tr>
<tr>
<td></td>
<td>• Magnesium-OH / Magnesiumcarbonate</td>
</tr>
<tr>
<td></td>
<td>• Niacin / Nicotinamide*</td>
</tr>
<tr>
<td></td>
<td>• Fe-Mg-hydroxycarbonate**</td>
</tr>
<tr>
<td></td>
<td>• Fe-(III)-oxid-OH**</td>
</tr>
<tr>
<td></td>
<td>• Colestilan**</td>
</tr>
<tr>
<td></td>
<td>• Salivary binders...</td>
</tr>
</tbody>
</table>

*Phosphate transport inhibitor (no binder)

**in pivotal studies
Phosphate binder therapy is associated with improved survival in incident dialysis patients

Estimated proportions:
- ca. 40% Ca-containing PB
- ca. 40% Sevelamer
- < 20% Lanthanum
- many combinations

Isakova T et al., JASN 2009; 20:388
RIND Study: Progression of coronary artery calcifications in incident hemodialysis patients

Block GA et al., Kidney Int 2005; 68:1815

**RANDOMISATION** within 90 days (start of HD)

- **Dialysate Ca=1.25 mmol/L**
- **“Usual” clinical practice**
- **Sevelamer**
- **“Extended treatment”**

- **Calcium-binder**
- **“Extended treatment”**

- **0 EBCT scan**
  - Dose titration
  - P <6.5 mg/dL
  - Ca$^{2+}$ <10.2 mg/dL

- **6 Mo 12 Mo 18 Mo EBCT scans**
  - Dose titration
  - P <6.5 mg/dL
  - Ca$^{2+}$ <10.2 mg/dL
  - PTH 150-300 pg/mL

- Renagel patients were allowed to receive nightly Ca supplements.
The absolute rise of CACS (median) after 18 months was 11-fold increased in the Ca salt vs. the sevelamer group!

„Progressors“ (60%) were already calcified at the start of the study!

Patients w/out coronary calcifications at the start of the study (40%) remained free of calcification – despite intake of calcium-based binders!
Treatment of CKD-MBD: Phosphorus and Calcium

- **4.1.1.** In patients with CKD Stages 3-5, we suggest maintaining serum phosphorus in the normal range (2C). In patients with CKD Stage 5D, we suggest lowering elevated phosphorus levels towards the normal range (2C).
Treatment of CKD-MBD: Phosphorus and Calcium

- **4.1.4.** In patients with CKD Stages 3-5 (2D) and 5D (2B), we suggest using phosphate-binding agents in the treatment of hyperphosphatemia. It is reasonable that the choice of phosphate binder takes into account CKD stage, presence of other components of CKD-MBD, concomitant therapies, and side-effect profile *(not graded).*
Treatment of CKD-MBD: Phosphorus and Calcium

• **4.1.5.** In patients with CKD Stages 3-5D and hyperphosphatemia, we recommend restricting the dose of calcium-based phosphate binders and/or the dose of calcitriol or vitamin D analog in the presence of persistent or recurrent hypercalcemia (1B).

• In patients with CKD Stages 3-5D and hyperphosphatemia, we suggest restricting the dose of calcium-based phosphate binders in the presence of arterial calcification (2C) and/or adynamic bone disease (2C) and/or if serum PTH levels are persistently low (2C).
Sevelamer carbonate as a new option for treatment of hyperphosphatemia in CKD stages 3 – 5

- Same polymer backbone: Retains similar phosphate-binding capacity
- Salt change: Potentially improves buffering capacity
- Available as tablets and powder

Structures adapted from Renagel and Renvela Package Inserts.
KDOQI Clinical Practice Guidelines: Guideline 15 – Metabolic Acidosis

- **15-1** In CKD Stages 3, 4 and 5, the serum level of total CO\(_2\) should be measured.

- **15-1a** The frequency of these measurements should be based on the stage of CKD as shown in Table. (OPINION)

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>GFR Range (mL/min/1.73m(^2))</th>
<th>Frequency of Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>30-59</td>
<td>At least every 12 months</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>At least every 3 months</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
<td>At least every 3 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dialysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>At least every month</td>
</tr>
</tbody>
</table>

15-2 In these patients, serum levels of total CO\(_2\) (bicarbonate) should be maintained at ≥22 mEq/L (22 mmol/L). (EVIDENCE) If necessary, supplemental alkali salts should be given to achieve this goal. (OPINION)

KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. Available at http://www.kidney.org/professionals/KDOQI/guidelines_bone/Guide15.htm
Renvela Equivalence Study

Study Design

Multicenter, Double-blind, Randomized, Crossover Study

- Starting dose of Renvela or Renagel was based on most recently prescribed dose of
  Renagel during run-in period
- Stable doses of cinacalcet and vitamin D were maintained throughout the study

### Renvela Equivalence Study

**Baseline Laboratories**

<table>
<thead>
<tr>
<th></th>
<th>Renvela (N=73)</th>
<th>Renagel (N=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>4.6 ± 1.09</td>
<td>4.6 ± 1.13</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>9.3 ± 0.67</td>
<td>9.3 ± 0.66</td>
</tr>
<tr>
<td>Calcium x Phosphorus (mg²/dL²)</td>
<td>42.9 ± 10.19</td>
<td>42.4 ± 10.70</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.8 ± 0.31</td>
<td>3.8 ± 0.31</td>
</tr>
<tr>
<td>iPTH (pg/mL)*</td>
<td>245</td>
<td>249</td>
</tr>
</tbody>
</table>

*iPTH is presented as median.*

# Renvela Equivalence Study

## Efficacy Results

### Mean Serum Phosphorus Levels ± SD (mg/dL)

<table>
<thead>
<tr>
<th></th>
<th>Renvela (mean ± SD)</th>
<th>Renagel (mean ± SD)</th>
<th>Geometric LS Mean Ratio (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=56</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mg/dL</td>
<td>4.6 ± 0.9</td>
<td>4.7 ± 0.9</td>
<td>0.99 (0.95 – 1.03)*</td>
</tr>
</tbody>
</table>

*90% CI for the ratio is within the interval 0.80-1.25
LS=Least Square

Renvela Equivalence Study
Serum Phosphorus During Washout Period

Mean Change in Serum P (mg/dL)

*Wilcoxon signed rank test used to compare change from baseline.
†All patients who completed washout regardless of form of sevelamer prescribed during treatment period.

**Renvela Equivalence Study**

**Effect of Treatment on Serum Bicarbonate**

*Wilcoxon signed rank test used to compare change from baseline within treatment.
†Wilcoxon signed rank test used to compare change from baseline between treatments.
All baseline values are post-5-weeks run-in on Renagel.


KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, Guideline 15 – Metabolic Acidosis.

![Bicarbonate Levels](chart.png)
# Renvela Equivalence Study

## Adverse Events*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th><strong>Renvela</strong></th>
<th></th>
<th><strong>Renagel</strong></th>
<th></th>
<th></th>
<th><strong>P-value</strong>†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>N=73</strong></td>
<td><strong>Patients N (%)</strong></td>
<td><strong>Events N</strong></td>
<td><strong>N=78</strong></td>
<td><strong>Patients N (%)</strong></td>
<td><strong>Events N</strong></td>
</tr>
<tr>
<td>Any Gastrointestinal Event</td>
<td>15 (20.5)</td>
<td>25</td>
<td>28 (35.9)</td>
<td>45</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (9.6)</td>
<td>9</td>
<td>10 (12.8)</td>
<td>13</td>
<td>0.467</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (8.2)</td>
<td>7</td>
<td>8 (10.3)</td>
<td>8</td>
<td>0.527</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (2.7)</td>
<td>3</td>
<td>5 (6.4)</td>
<td>6</td>
<td>0.257</td>
<td></td>
</tr>
<tr>
<td>GERD</td>
<td>1 (1.4)</td>
<td>1</td>
<td>4 (5.1)</td>
<td>5</td>
<td>0.180</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>0 (0.0)</td>
<td>0</td>
<td>3 (3.8)</td>
<td>3</td>
<td>0.083</td>
<td></td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1 (1.4)</td>
<td>1</td>
<td>3 (3.8)</td>
<td>3</td>
<td>0.317</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (2.7)</td>
<td>2</td>
<td>1 (1.3)</td>
<td>1</td>
<td>0.564</td>
<td></td>
</tr>
</tbody>
</table>

*Occurring in ≥2% of patients; †McNemar’s Test.

GERD=Gastroesophageal Reflux Disease

Sevelamer carbonate (Renvela) in patients in CKD stages 4-5

Ketteler M et al., CJASN 2008

Screened: n=141 (incl 12 re-screened)

Screen/washout failure: n=92

Entered Treatment Phase: n=49

Discontinued:
  Adverse event: n=4
  Wished to withdraw: n=2
  Other reason: n=2

Completed Study: n=41
GFR for all patients (PPS – SVCARB00105)

Calculated GFR (C-G)

Patient result

Stage 4 CKD
Stage 5 CKD
Sevelamer carbonate (Renvela) in patients in CKD stages 4-5

Ketteler M et al., CJASN 2008
# Sevelamer carbonate (Renvela) in patients in CKD stages 4-5

Ketteler M et al., CJASN 2008

<table>
<thead>
<tr>
<th>Laboratory parameter (serum)</th>
<th>Pre-washout $^\dagger$</th>
<th>Baseline</th>
<th>Day 56/ET</th>
<th>Change from Baseline to Day 56/ET</th>
<th>P-value*</th>
<th>Post-washout</th>
<th>Change from Day 56 to Day 70</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>-</td>
<td>16.6 ± 3.6</td>
<td>18.2 ± 3.7</td>
<td>1.3 ± 2.9</td>
<td>0.005</td>
<td>18.0 ± 3.6</td>
<td>-0.5 ± 3.5</td>
<td>0.326</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>9.1</td>
<td>8.5</td>
<td>8.8</td>
<td>0.3</td>
<td>&lt;0.001</td>
<td>8.6</td>
<td>-0.2</td>
<td>0.007</td>
</tr>
<tr>
<td>iPTH (pg/mL) median</td>
<td>208</td>
<td>341</td>
<td>319</td>
<td>-39</td>
<td>0.013</td>
<td>362</td>
<td>63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>25-OH Vit D (ng/mL)</td>
<td>28.1 ± 18.8</td>
<td>28.9 ± 16.2</td>
<td>31.1 ± 12.9</td>
<td>2.0 ± 10.3</td>
<td>0.080</td>
<td>32.3 ± 13.7</td>
<td>0.2 ± 7.7</td>
<td>0.890</td>
</tr>
<tr>
<td>1,25 (OH)$_2$ Vit D (pg/mL)</td>
<td>-</td>
<td>25.4 ± 10.1</td>
<td>31.8 ± 12.1</td>
<td>5.3 ± 14.9</td>
<td>0.026</td>
<td>31.8 ± 11.7</td>
<td>-0.3 ± 14.4</td>
<td>0.942</td>
</tr>
</tbody>
</table>
Sevelamer carbonate provides a differential of ~ + 4mmol/L in serum bicarbonate in CKD patients not on dialysis in comparison with sevelamer hydrochloride.

<table>
<thead>
<tr>
<th>Phosphate Binder</th>
<th>CKD patients not on dialysis Change from baseline in serum bicarbonate level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevelamer carbonate (SVCARB00105)</td>
<td>+1.3 ± 2.9 mmol/L*</td>
</tr>
<tr>
<td>Sevelamer hydrochloride (GTC-45-204)</td>
<td>−2.6 ± 4.6 mmol/L**</td>
</tr>
</tbody>
</table>

* 8 weeks treatment, ** 12 weeks treatment
Early management of phosphate regulation

Conclusions

✓ Sevelamer carbonate is a non-absorbable phosphate binder equivalent to sevelamer HCl in controlling serum phosphorus (availability: tablets & powder formulation)

✓ Sevelamer carbonate is acid/base-neutral

✓ Sevelamer carbonate is well-tolerated and was associated with a significantly lower number of patients with GI adverse events than sevelamer HCl

✓ Lipid profiles are favorable with sevelamer carbonate treatment

✓ Sevelamer carbonate appears as an safe, effective and feasible first choice for treatment of hyperphosphatemia in both predialysis and dialysis CKD stages

A randomized double-blind pilot study of serum phosphorus normalization in chronic kidney disease: A new paradigm for clinical outcomes studies in nephrology

- Do you believe that a randomized clinical trial of target levels of serum phosphorus is necessary in patients with CKD? Is it achievable in patients with stage 5D CKD? Can it be placebo controlled?
- Do you believe that serum phosphorus is the most appropriate measure to use as a primary outcome variable for such a randomized clinical trial?
- Do you believe that it is important to compare at least 1 noncalcium phosphate binder and at least 1 calcium-containing phosphate binder in addition to placebo in such a trial?
- What would be the most compelling result from such a trial that would demand that clinical practice change to target lower serum phosphorus values in all patients with CKD?