EVOLVE

EValuation Of Cinacalcet HCl Therapy to Lower CardioVascular Events™


EVOLVE

EValuation Of Cinacalcet Therapy to Lower Cardiovascular Events


Higher PTH Is Associated with Mortality

Hypothesis

Treatment with cinacalcet reduces the risks of death and nonfatal cardiovascular events among hemodialysis patients with secondary hyperparathyroidism.
Study Schema

Trial Population
- Hemodialysis
- iPTH ≥ 300 pg/mL
- Ca ≥ 8.4 mg/dL
- Ca x P ≥ 45 mg^2/dL^2

Placebo plus standard of care (n = 1900)
- Randomized (1:1), double blind, placebo controlled
- Event-driven: 1882 events needed for 88% power to detect a 20% treatment effect at an alpha level of 0.044

Cinacalcet plus standard of care (n = 1900)

Primary endpoint
Time to the primary composite endpoint comprising: all-cause mortality or non-fatal cardiovascular events (myocardial infarction, hospitalization for unstable angina, heart failure, peripheral vascular event)

Secondary endpoints
Fracture, PTX, CV death, stroke; components of primary composite endpoint
EVOLVE – a global mega-trial

20050182 Study—Largest Prospective Global Clinical Trial Ever Conducted in the Dialysis Population

4 Continents—22 Participating Countries

~ 180 Sites
1430 Subjects

~ 24 Sites
146 Subjects

~ 19 Sites
149 Subjects

~ 73 Sites
686 Subjects

~ 183 Sites
1189 Subjects

~ 21 Sites
283 Subjects

Totaling 458 Sites and 3,883 Subjects

Data on file, Amgen.
Subject Disposition & Baseline Demographics
### Baseline Demographic and Clinical Characteristics by Region

<table>
<thead>
<tr>
<th>Region</th>
<th>Australia (N = 149)</th>
<th>Canada (N = 146)</th>
<th>Europe (N = 1188)</th>
<th>Latin America (N = 687)</th>
<th>Russia (N = 283)</th>
<th>USA (N = 1430)</th>
<th>Total* (N = 3883)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years – mean</td>
<td>59.6</td>
<td>57.5</td>
<td>57.1</td>
<td><strong>48.5</strong></td>
<td>49.9</td>
<td>55.1</td>
<td><strong>54.4</strong></td>
</tr>
<tr>
<td>Sex, female — %</td>
<td>34.9%</td>
<td>39.0%</td>
<td>39.0%</td>
<td>39.3%</td>
<td>48.4%</td>
<td>41.9%</td>
<td>40.6%</td>
</tr>
<tr>
<td>Race/ethnicity — %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>85.9%</td>
<td>67.8%</td>
<td>92.9%</td>
<td>36.2%</td>
<td>100.0%</td>
<td><strong>26.4%</strong></td>
<td><strong>57.7%</strong></td>
</tr>
<tr>
<td>Black</td>
<td>0.0%</td>
<td>11.6%</td>
<td>3.2%</td>
<td>7.9%</td>
<td>0.0%</td>
<td>50.9%</td>
<td>21.6%</td>
</tr>
<tr>
<td>Other</td>
<td>14.1%</td>
<td>20.5%</td>
<td>3.9%</td>
<td>55.9%</td>
<td>0.0%</td>
<td>22.7%</td>
<td>20.7%</td>
</tr>
<tr>
<td>BMI, kg/m² – mean</td>
<td><strong>28.5</strong></td>
<td><strong>29.4</strong></td>
<td>26.5</td>
<td>25.5</td>
<td>25.7</td>
<td><strong>29.6</strong></td>
<td><strong>27.6</strong></td>
</tr>
<tr>
<td>Dialysis vintage, months – median</td>
<td>39</td>
<td>53</td>
<td>44</td>
<td><strong>64</strong></td>
<td><strong>72</strong></td>
<td>34.5</td>
<td><strong>45</strong></td>
</tr>
</tbody>
</table>

BMI, body mass index; ECG, electrocardiogram; DBP, diastolic blood pressure; SBP, systolic blood pressure.

*Comparisons across all regions were significant at P < 0.0001 except for sex.

## Baseline Demographic and Clinical Characteristics by Region, continued

<table>
<thead>
<tr>
<th>Region</th>
<th>Australia (N = 149)</th>
<th>Canada (N = 146)</th>
<th>Europe (N = 1188)</th>
<th>Latin America (N = 687)</th>
<th>Russia (N = 283)</th>
<th>USA (N = 1430)</th>
<th>Total* (N = 3883)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular disease—%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>96.6%</td>
<td>97.9%</td>
<td>92.7%</td>
<td>88.9%</td>
<td>87.6%</td>
<td>98.3%</td>
<td>94.1%</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>96.6%</td>
<td>97.9%</td>
<td>88.1%</td>
<td>87.0%</td>
<td>85.2%</td>
<td>97.6%</td>
<td>91.8%</td>
</tr>
<tr>
<td><strong>Coronary artery bypass graft</strong></td>
<td>16.8%</td>
<td>11.6%</td>
<td>7.2%</td>
<td>3.1%</td>
<td>0.4%</td>
<td>9.7%</td>
<td>7.4%</td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22.8%</td>
<td>23.3%</td>
<td>13.4%</td>
<td>5.5%</td>
<td>7.8%</td>
<td>13.6%</td>
<td>12.4%</td>
</tr>
<tr>
<td><strong>Heart failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>28.2%</td>
<td>21.9%</td>
<td>17.1%</td>
<td>9.6%</td>
<td>19.8%</td>
<td>35.4%</td>
<td>23.3%</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>10.7%</td>
<td>8.9%</td>
<td>9.4%</td>
<td>4.1%</td>
<td>7.8%</td>
<td>11.2%</td>
<td>9.0%</td>
</tr>
<tr>
<td><strong>Transient ischemic attack</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>8.1%</td>
<td>11.0%</td>
<td>5.7%</td>
<td>2.0%</td>
<td>4.2%</td>
<td>3.6%</td>
<td>4.5%</td>
</tr>
<tr>
<td><strong>Peripheral arterial disease</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24.8%</td>
<td>26.7%</td>
<td>19.2%</td>
<td>6.3%</td>
<td>6.0%</td>
<td>19.0%</td>
<td>16.4%</td>
</tr>
<tr>
<td><strong>Amputation</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8.1%</td>
<td>8.2%</td>
<td>5.0%</td>
<td>2.3%</td>
<td>2.1%</td>
<td>10.1%</td>
<td>6.4%</td>
</tr>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20.8%</td>
<td>14.4%</td>
<td>15.5%</td>
<td>4.8%</td>
<td>7.4%</td>
<td>9.5%</td>
<td>11.0%</td>
</tr>
</tbody>
</table>

BMI, body mass index; ECG, electrocardiogram; DBP, diastolic blood pressure; SBP, systolic blood pressure.

*Comparisons across all regions were significant at P < 0.0001 except for sex.

Biochemical Values for Subjects by Region*

<table>
<thead>
<tr>
<th>Mean (units)†</th>
<th>Australia (N = 149)</th>
<th>Canada (N = 146)</th>
<th>Europe (N = 1188)</th>
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<th>Russia (N = 283)</th>
<th>USA (N = 1430)</th>
<th>Total (N = 3883)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL (mg/dL)</td>
<td>86.5</td>
<td>72.0</td>
<td>95.8</td>
<td>93.7</td>
<td>123.6</td>
<td>81.0</td>
<td>90.7</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>42.6</td>
<td>43.8</td>
<td>42.8</td>
<td>41.2</td>
<td>42.2</td>
<td>45.2</td>
<td>43.3</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>161.8</td>
<td>146.9</td>
<td>173.3</td>
<td>166.9</td>
<td>204.4</td>
<td>156.5</td>
<td>166.8</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>137.0</td>
<td>124.5</td>
<td>149.0</td>
<td>140.0</td>
<td>162.0</td>
<td>125.5</td>
<td>139.0</td>
</tr>
<tr>
<td>Serum calcium (mg/dL)</td>
<td>9.9</td>
<td>9.9</td>
<td>9.7</td>
<td>9.9</td>
<td>10.0</td>
<td>9.8</td>
<td>9.8</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dL)</td>
<td>6.4</td>
<td>6.2</td>
<td>6.4</td>
<td>6.6</td>
<td>7.0</td>
<td>6.4</td>
<td>6.5</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>769.5</td>
<td>749.3</td>
<td>713.0</td>
<td>987.5</td>
<td>846.0</td>
<td>547.5</td>
<td>691.8</td>
</tr>
</tbody>
</table>

LDL, low-density lipoprotein; HDL, high-density lipoprotein; BUN, blood urea nitrogen; BCE, bone collagen equivalent.
*3 Latin American nations and 15 individual European nations. Comparisons across all regions were significant at P < 0.0001 except for serum sodium/PTH.
†Mean are presented for normally distributed data; otherwise, median are used for non-normally distributed data.

Cardiovascular Results
Kaplan-Meier Plot of Primary Composite Endpoint (Intent-to-treat Analysis)

Hazard ratio, 0.93 (95% CI, 0.85, 1.02)
Log-rank, $p = 0.112$

Subjects at risk:
- Placebo: 1935, 1804, 1693, 1579, 1476, 1384, 1312, 1224, 1160, 1109, 1053, 996, 940, 650, 404, 114
- Cinacalcet: 1948, 1842, 1739, 1638, 1556, 1472, 1384, 1303, 1230, 1177, 1115, 1051, 989, 679, 399, 113

Proportion Event-free vs. Time (months)
Kaplan-Meier Plot of All-Cause Mortality (Intent-to-treat Analysis)

Hazard ratio, 0.94 (95% CI, 0.85, 1.04)
Log-rank, $p = 0.249$

Subjects at risk:
- Placebo: 1935, 1882, 1828, 1754, 1694, 1622, 1559, 1486, 1426, 1388, 1334, 1283, 1232, 866, 537, 162
- Cinacalcet: 1948, 1903, 1845, 1779, 1736, 1680, 1621, 1565, 1507, 1462, 1412, 1354, 1292, 899, 546, 167
Two issues came up in EVOLVE:

#1: an unexpected age difference between the two EVOLVE study arms

Hugh Hefner and his fiancee, Playboy Playmate Crystal Harris
ibtimes.com
# The age difference in EVOLVE...

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison</th>
<th>N=</th>
<th>Age: intervent.</th>
<th>Age: controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROCKET AF (2011)</td>
<td>Rivaroxaban vs Warfarin</td>
<td>&gt;14.000</td>
<td>73.0 (median)</td>
<td>73.0</td>
</tr>
<tr>
<td>IDEAL (2010)</td>
<td>Early versus Late Dialysis</td>
<td>828</td>
<td>60.2 (mean)</td>
<td>60.5</td>
</tr>
<tr>
<td>AURORA (2009)</td>
<td>Rosuvastatin in Dialysis</td>
<td>2773</td>
<td>64.1 (mean)</td>
<td>64.3</td>
</tr>
<tr>
<td>4D (2005)</td>
<td>Atorvastatin in Diabetes &amp; HD</td>
<td>1255</td>
<td>65.7 (mean)</td>
<td>65.7</td>
</tr>
<tr>
<td>SHARP (2011)</td>
<td>Simvastatin + Ezetimibe in CKD &amp; HD</td>
<td>9438</td>
<td>62.0 (mean)</td>
<td>62.0</td>
</tr>
<tr>
<td>DCOR (2007)</td>
<td>Sevelamer in Dialysis</td>
<td>2103</td>
<td>61.0 (median)</td>
<td>62.0</td>
</tr>
<tr>
<td>TREAT (2009)</td>
<td>Darbe vs Pbo in T2D and CKD</td>
<td>4038</td>
<td>68 (median)</td>
<td>68</td>
</tr>
<tr>
<td>FHN (2010)</td>
<td>Frequent Hemodialysis</td>
<td>245</td>
<td>48.9 (mean)</td>
<td>52.0</td>
</tr>
<tr>
<td>CHARM (2003)</td>
<td>Candesartan in Heart Failure</td>
<td>7599</td>
<td>65.9 (mean)</td>
<td>66</td>
</tr>
<tr>
<td>RENAAL (2001)</td>
<td>Losartan in T2D and CKD</td>
<td>1513</td>
<td>60 (mean)</td>
<td>60</td>
</tr>
<tr>
<td>PRAISE (1996)</td>
<td>Amlodipine in severe CHF</td>
<td>1153</td>
<td>64.7 (mean)</td>
<td>64.7</td>
</tr>
<tr>
<td>MIRACL (2001)</td>
<td>Atorvastatin in Acute Coronary Syndrome</td>
<td>3086</td>
<td>65 (mean)</td>
<td>65</td>
</tr>
<tr>
<td><strong>EVOLVE</strong></td>
<td>Cinacalcet in Dialysis</td>
<td>3883</td>
<td>54.8 (mean)</td>
<td>54.0 (median)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>55.0 (median)</td>
<td></td>
</tr>
</tbody>
</table>
...is a function of the standard deviation

| Standard Deviation for Age | Probability $|\text{Age}_{\text{tx}} - \text{Age}_{\text{control}}| >0.8$ Yrs | Example Trial Populations |
|---------------------------|----------------------------------------|-----------------------------|
| 20                        | 0.20                                   | EVOLVE, HEMO, Cinacalcet Ph3, DCOR |
| 14                        | 0.08                                   | SHARP                       |
| 12                        | 0.04                                   |                             |
| 11                        | 0.02                                   | CHARM, MIRACLE, PRAISE, RED-HF |
| 10                        | 0.01                                   | TREAT                       |
| 8                         | 0                                      | 4D, AURORA                  |

Higher standard deviations in sHPT patient populations than in cardiovascular outcome studies.
## Unadjusted and Adjusted ITT Analyses

<table>
<thead>
<tr>
<th>Model</th>
<th>Relative Hazard</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>0.93</td>
<td>0.85 to 1.02</td>
<td>0.11</td>
</tr>
<tr>
<td>Adjusted for age alone</td>
<td>0.88</td>
<td>0.81 to 0.97</td>
<td>0.007</td>
</tr>
<tr>
<td>Multivariable* (best fit)</td>
<td>0.88</td>
<td>0.79 to 0.97</td>
<td>0.008</td>
</tr>
<tr>
<td>Multivariable*-adjusted (all included)</td>
<td>0.88</td>
<td>0.80 to 0.98</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* - 40 covariates included
Two issues came up in EVOLVE:

#2: an expected cross-over between treatments
Time to First Discontinuation of Study Drug due to Protocol-specified Reasons*

Subjects at risk:

- Placebo:
  - year1: 1938
  - year2: 1686
  - year3: 1491
  - year4: 1312
  - year5: 1180

- Cinacalcet:
  - year1: 1923
  - year2: 1667
  - year3: 1419
  - year4: 1211
  - year5: 1180

*Safety Analysis Set
Time to First Discontinuation from Study Drug due to Non-protocol Specified Reasons*

Subjects at risk:

Placebo

Cinacalcet

Proportion of Subjects Off IP

Time (months)

*Safety Analysis Set
Intention-to-treat versus censored versus lag censored analysis

**ITT**
- Includes all data until study termination
- Stop → Event

**Censored**
- On IP
- Stop
- Event → Censored data

**Lag censored**
- Patient data analyzed until 6 months after end of study medication
- Stop → Event → Censored data

6 M
Lag-Censoring Analysis:
Effect of lag duration on primary end point

<table>
<thead>
<tr>
<th>Lag duration (months)</th>
<th>Cinacalcet (N=1948)</th>
<th>Placebo (N=1935)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>423</td>
<td>463</td>
<td>0.79 (0.69, 0.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3</td>
<td>594</td>
<td>616</td>
<td>0.83 (0.74, 0.93)</td>
<td>0.002</td>
</tr>
<tr>
<td>6</td>
<td>638</td>
<td>658</td>
<td>0.85 (0.76, 0.95)</td>
<td>0.003</td>
</tr>
<tr>
<td>9</td>
<td>672</td>
<td>692</td>
<td>0.86 (0.77, 0.96)</td>
<td>0.005</td>
</tr>
<tr>
<td>12</td>
<td>705</td>
<td>722</td>
<td>0.87 (0.78, 0.96)</td>
<td>0.008</td>
</tr>
<tr>
<td>18</td>
<td>772</td>
<td>768</td>
<td>0.91 (0.82, 1.00)</td>
<td>0.054</td>
</tr>
</tbody>
</table>
Kaplan-Meier Plot of Primary Composite Endpoint
(Lag Censoring Analysis)

Hazard ratio, 0.85 (95% CI, 0.76, 0.95)
Log-rank, $p = 0.003$

Subjects at risk:
- Placebo: 1935 1789 1615 1299 1080 875 739 625 525 474 419 353 303 180 93 26
- Cinacalcet: 1948 1835 1627 1376 1179 1002 847 731 632 551 491 425 362 239 130 28
Kaplan-Meier Plot of All-Cause Mortality
(Lag Censoring Analysis)

Hazard ratio, 0.83 (95% CI, 0.73, 0.96)
Log-rank, $p = 0.009$

Subjects at risk:
- Placebo: 1935, 1861, 1729, 1422, 1211, 1004, 867, 743, 628, 567, 499, 429, 380, 234, 119, 33
- Cinacalcet: 1948, 1890, 1717, 1474, 1282, 1113, 967, 857, 757, 663, 597, 518, 452, 293, 167, 42
Summary of Adverse Events

- Exposure-adjusted rates (per 100 patient-years), cinacalcet v. placebo
  - Serious AE [53.3 v. 56.9]
  - All AE [273.2 v. 217.8]*
  - Hypocalcemia [6.7 v. 0.9]*
  - Nausea [18.3 v. 9.1]*
  - Vomiting [15.4 v. 8.0]*
  - Neoplastic events [2.9 v. 2.5]
  - Seizure [1.2 v. 0.8]

- 7-fold increase in hypocalcemia
- 2-fold increase in nausea/vomiting
Mineral Bone Disease Results
Biochemical Parameters During the Study (ITT)

**Median iPTH**
- Placebo: Blue dots
- Cinacalcet: Pink dots

**Median Serum Calcium**

**Median Serum Phosphate**

**Median Ca x P Product**
Concomitant Medications Over Time in Cinacalcet-or Placebo-Treated Patients While Receiving Study Drug

IV Paricalcitol-equivalent dose is calculated using the following: 2 mcg Paricalcitol (IV) = 1 mcg Doxercalciferol (IV) = 1 mcg Alfacalcidol (IV) = 0.5 mcg Calcitriol (IV) = 1 mcg Paricalcitol (PO) = 0.5 mcg Alfacalcidol (PO) = 0.25 mcg Calcitriol (PO)

N = Number of patients who received at least one dose of study drug; n = Number of patients with study assessment at the study visit; IV = intravenous; PO = oral
**Time to First Parathyroidectomy or Time to First Episode of Severe Unremitting HPT (ITT)**

### Severe, unremitting HPT
- Pre-specified and defined as
  - PTH > 1000 pg/mL (106.0 pmol/L) with serum calcium > 10.5 mg/dL (2.6 mmol/L) on 2 consecutive occasions
  - OR
  - PTH > 1000 pg/mL with serum calcium >10.5 mg/dL on a single occasion and subsequent commercial cinacalcet use within 2 months of the laboratory assessment
  - OR
  - parathyroidectomy

**Time to First Parathyroidectomy**

- Hazard ratio, 0.44 (95% CI, 0.36, 0.54)
- Log-rank, $p<0.001$

**Time to First Episode of Severe Unremitting HPT**

- Hazard ratio, 0.43 (95% CI, 0.37, 0.50)
- Log-rank, $p<0.001$
Kaplan-Meier Plots for Time to First Clinical Fracture (Intent-to-treat Analysis)

Hazard ratio, 0.89 (95% CI, 0.75, 1.07)
Log-rank, $p = 0.218$

N = Number of patients in the intent-to-treat analysis set; n = Number of patients with laboratory value at the study visit
Calciphylaxis (calcific uremic arteriolopathy)

6 cases in cinacalcet-treated patients
18 cases in placebo-treated patients

⇒ exposure-adjusted rate per 100 patient-years:
0.1 (cinacalcet) versus 0.5 (placebo)  \( p=0.009 \)
Conclusions

• Unadjusted intent-to-treat approach: 7% reduction in the risk of death or major cardiovascular events (myocardial infarction, hospitalization for unstable angina, heart failure and peripheral vascular events), a non-significant (non-definitive) result.

• Adjusting for age, or age + other characteristics ⇒ nominally significant 12% reduction in the risk of death or major cardiovascular events. With lag censoring, the effects were more pronounced.

• Cinacalcet significantly reduces rates of parathyroidectomy and severe, unremitting hyperparathyroidism.

• Any potential benefits must be balanced against risks and discomforts.
WHAT NOW?
Therapy of Secondary Hyperparathyroidism in CKD 5

Convincing evidence from RCTs suggesting clinical benefit:

- None
- Some but non-definitive
- Definitive

**Step 1:**
Control S-PO$_4$

**Step 2:**
Vitamin-D

**Step 3:**
Specific Intervention

- Diet
  - Adjust Dialysis
  - PO$_4^-$ binder
  - Aluminum
  - Mg-contain.
  - Lanthanum
  - Ca-contain.
  - Sevelamer

- Native Vit-D
- Calcitriol, Alfacalcidol
- Pari-calcitol
- Doxercalciferol
- Parathyroidectomy
- Cinacalcet