# The EVOLVE-ing Spectrum of CKD-MBD



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KDIGO Controversies Conference on CKD-MBD

Disclosures: Amgen, Keryx, Ardelyx

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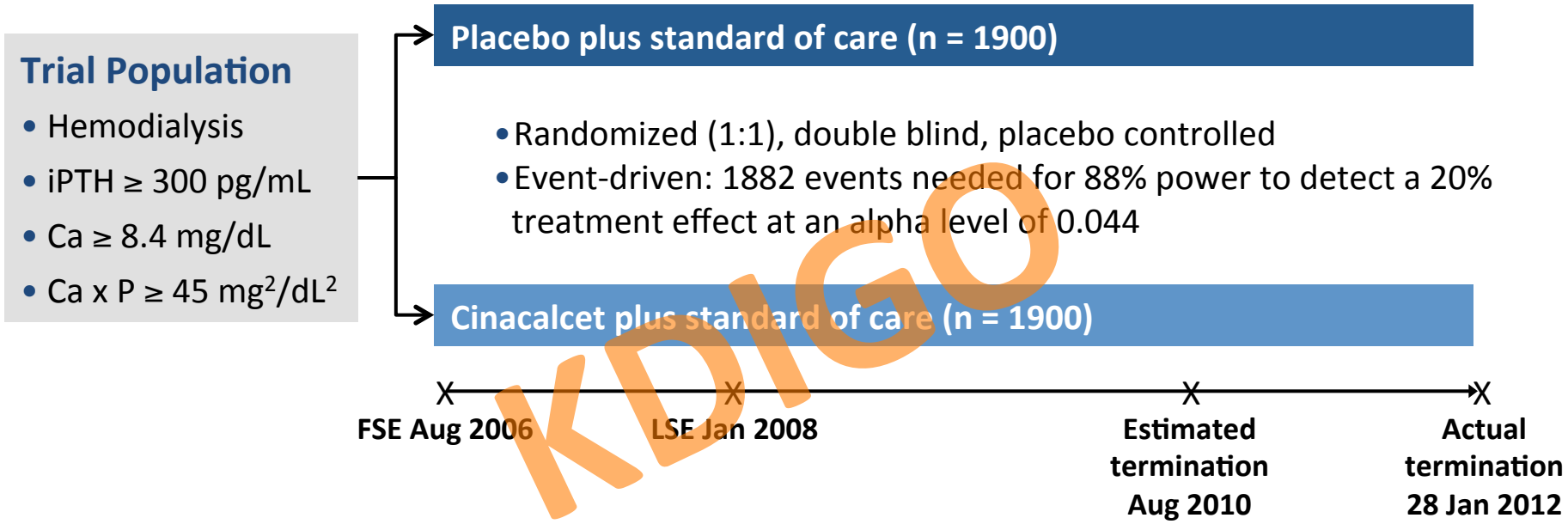
# Study Schema






## 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 or peripheral vascular event)

## Secondary endpoints

Fracture, PTX, CV death, stroke; components of primary composite endpoint

# Summary of Analytic Approach

- All endpoint data collected and analyzed in accordance with the intent-to-treat (ITT) principle
- Kaplan-Meier product limit estimates of event-free survival time; relative hazards and 95% confidence intervals computed from proportional hazards regression models, stratified by country and diabetes
- Age-adjusted, multivariable-adjusted and lag censoring analyses were pre-specified, as were analyses censoring at kidney transplantation, PTX and use of commercial cinacalcet

# Baseline Patient Characteristics

| Demographics | Cinacalcet (N = 1948) | Placebo (N = 1935) |
|---|---|---|
| **Age (yr) – median (p10, p90)** | **55.0** (35.0, 74.0) | **54.0** (35.0, 73.0) |
| **Female sex** | 41.5% | 39.7% |
| **Race or ethnic group** | | |
| White | 57.7% | 57.7% |
| Black | 21.0% | 22.1% |
| Other | 21.3% | 20.2% |
| **Quételet's (body mass) index ($kg/m^2$) – median (p10, p90)** | 26.3 (20.4, 36.4) | 26.4 (20.6, 36.7) |
| **Dialysis vintage (months) – median (p10, p90)** | 45.4 (8.5, 142.0) | 45.1 (9.9, 149.6) |
| **Blood pressure (mm Hg) – median (p10, p90)** | | |
| Systolic | 140 (110, 176) | 141 (111, 177) |
| Diastolic* | 80 (60, 100) | 80 (60, 100) |



N = Number of randomized patients. Percentages are based on N.
*p-value<0.05

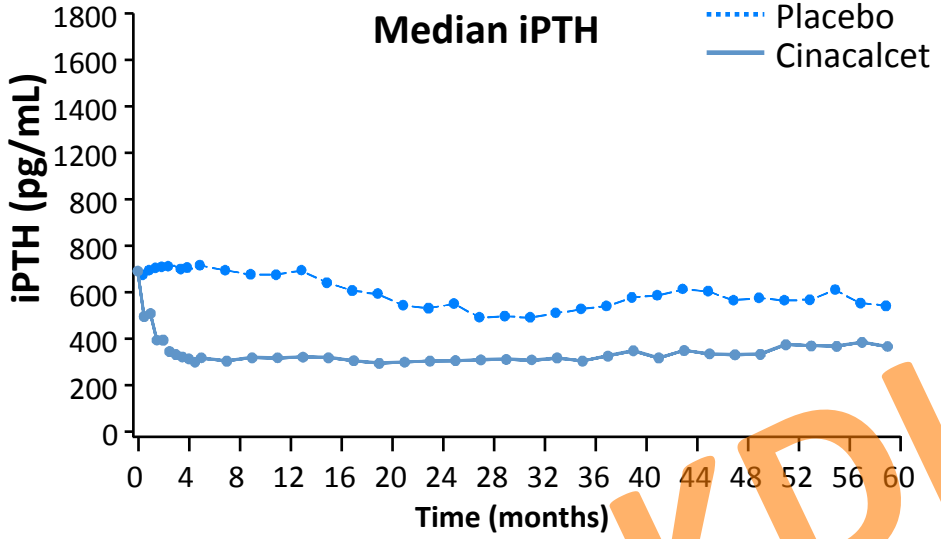
# Baseline Patient Characteristics

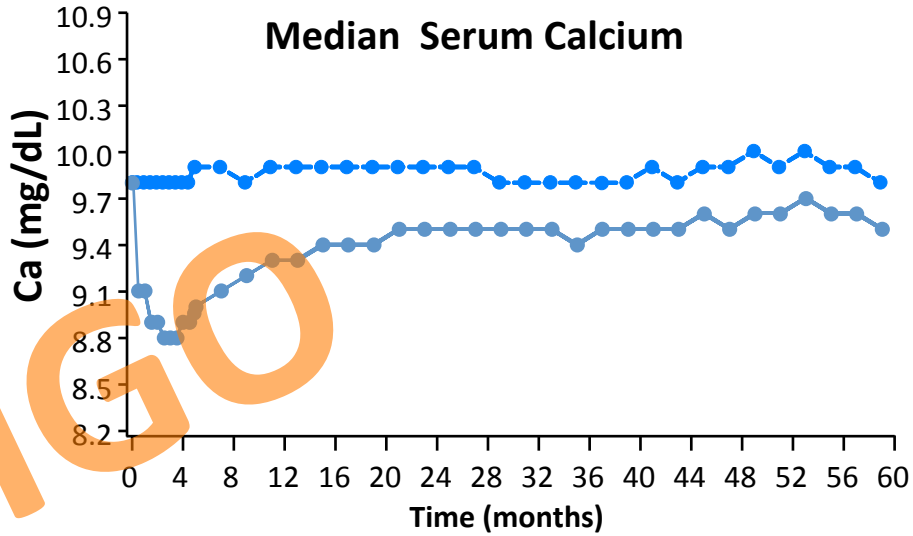
| Medical History | Cinacalcet (N = 1948) | Placebo (N = 1935) |
|---|---|---|
| **History of diabetes** | 33.6% | 33.5% |
| Type 1 | 3.7% | 4.2% |
| Type 2 | 29.8% | 29.4% |
| **History of cardiovascular disease** | 95.4% | 94.6% |
| Hypertension | 92.5% | 91.7% |
| Heart failure | 23.1% | 23.6% |
| Peripheral vascular disease | 16.1% | 16.6% |
| CABG | 6.9% | 8.0% |
| PCI | 6.7% | 6.8% |
| Myocardial infarction | 12.3% | 12.6% |
| Stroke | 8.3% | 10.0% |
| Transient ischemic attack* | 5.1% | 3.8% |
| Amputation | 6.2% | 6.7% |
| Atrial fibrillation | 10.4% | 11.6% |

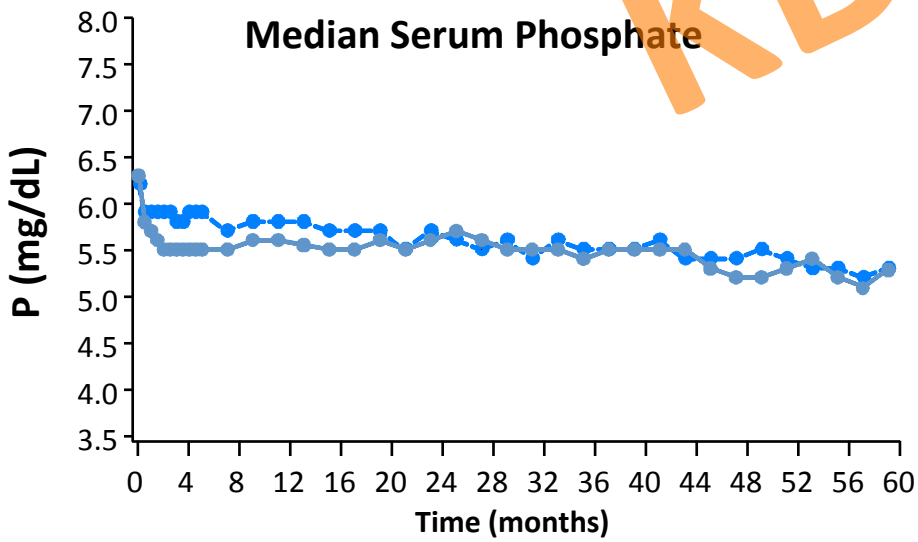


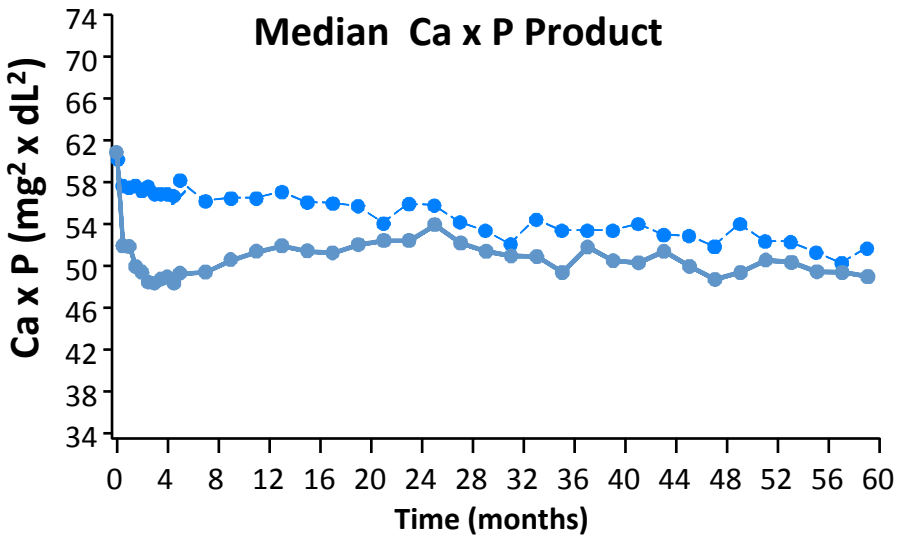
CABG = Coronary Artery Bypass Graft; PCI = Percutaneous coronary intervention
N = Number of randomized patients. Percentages are based on N.
*p-value<0.05

# Biochemical Parameters (ITT)

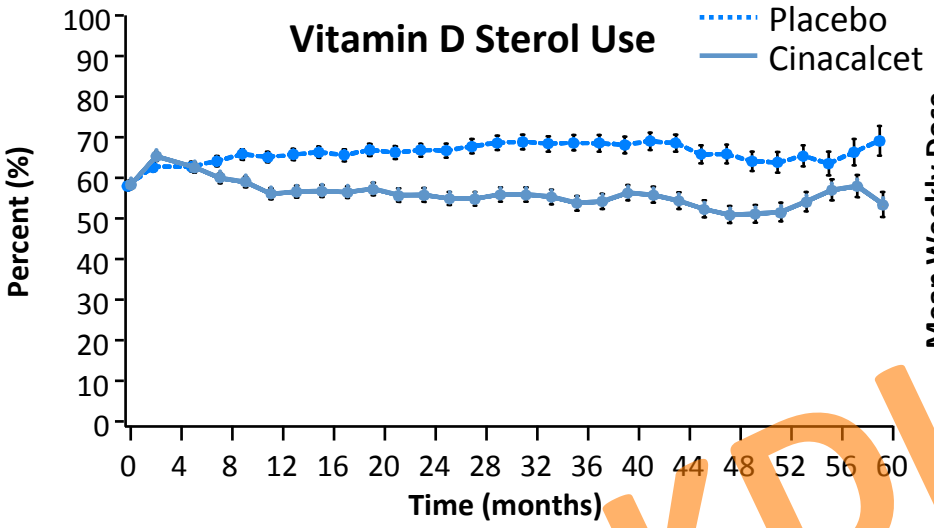


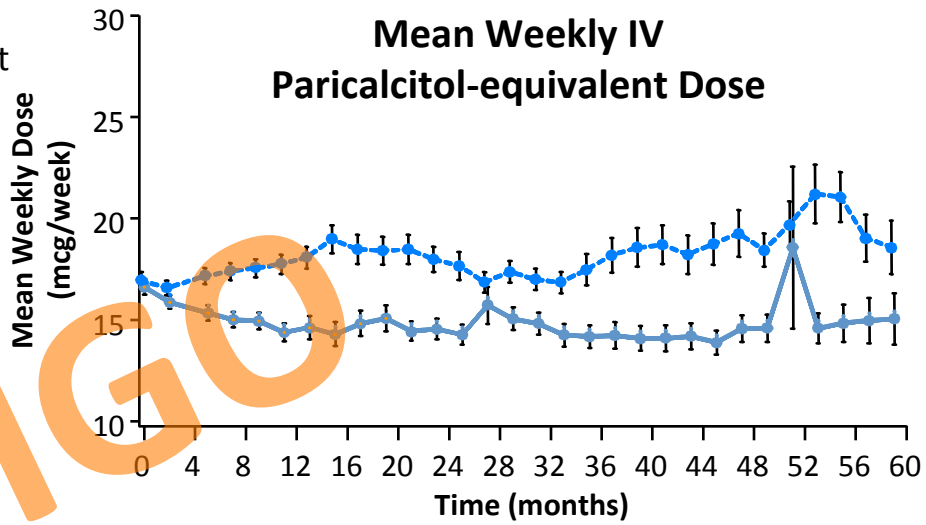



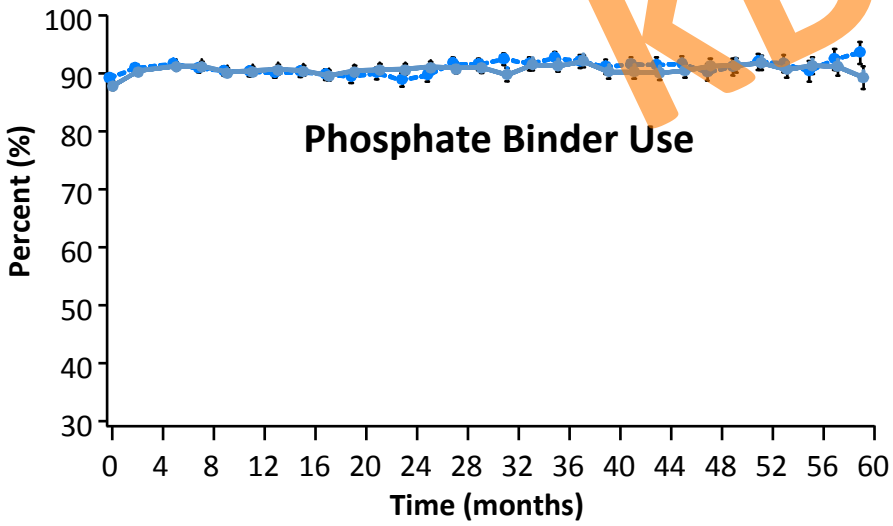



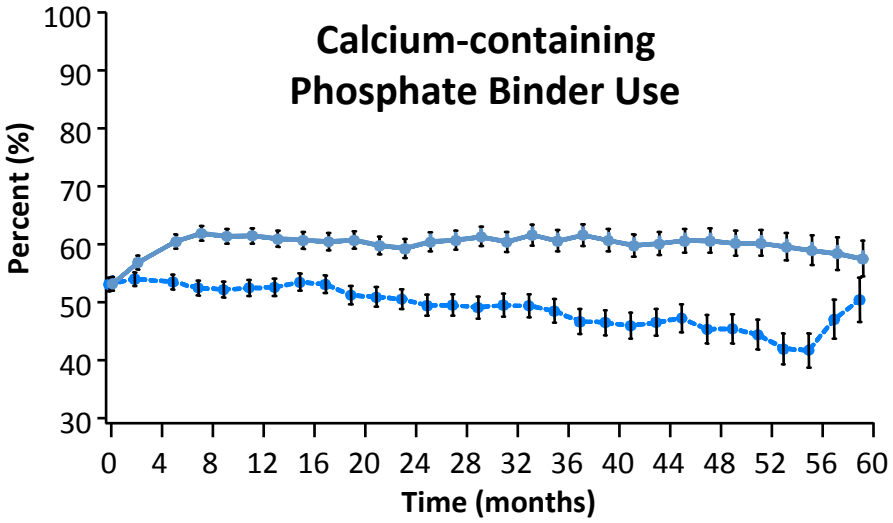



# P Binders and Vitamin D (ITT)



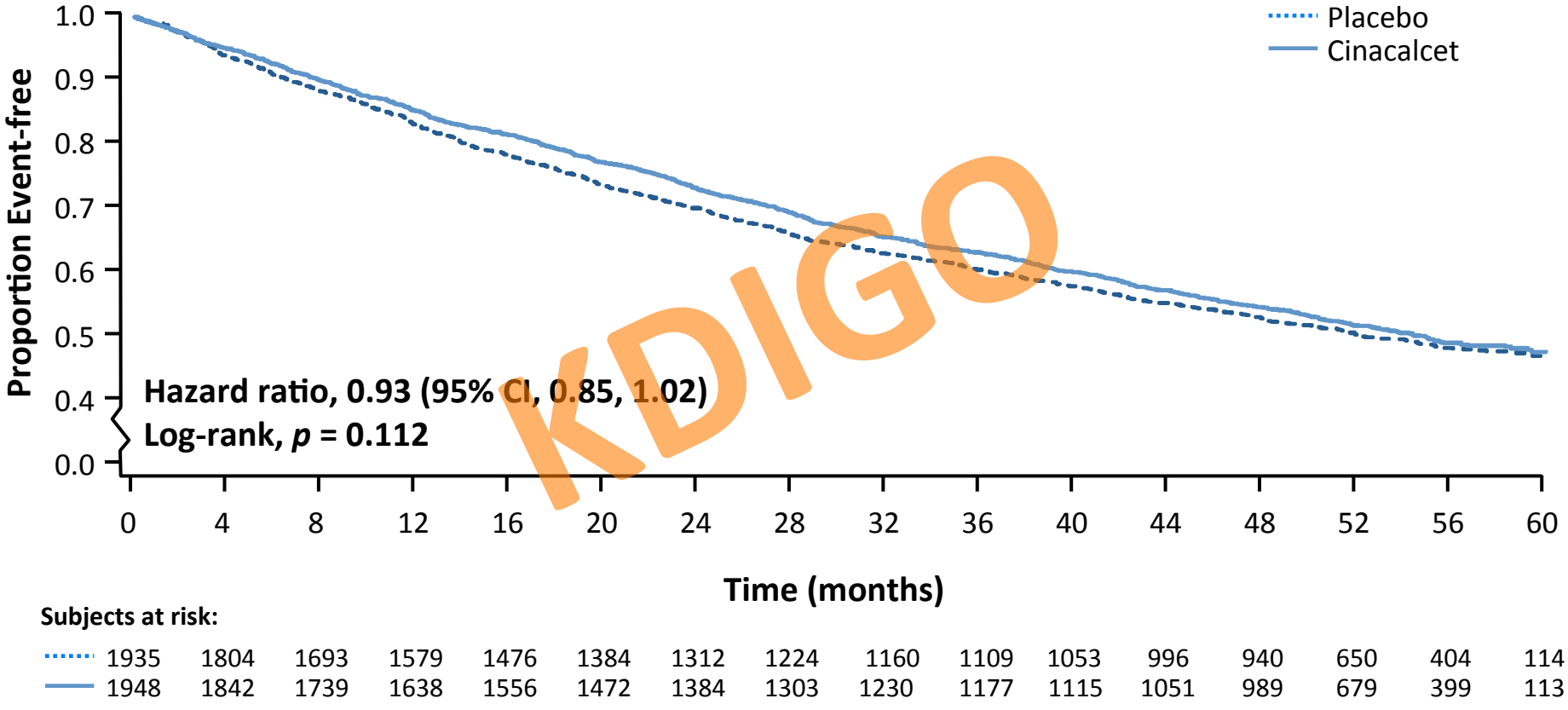





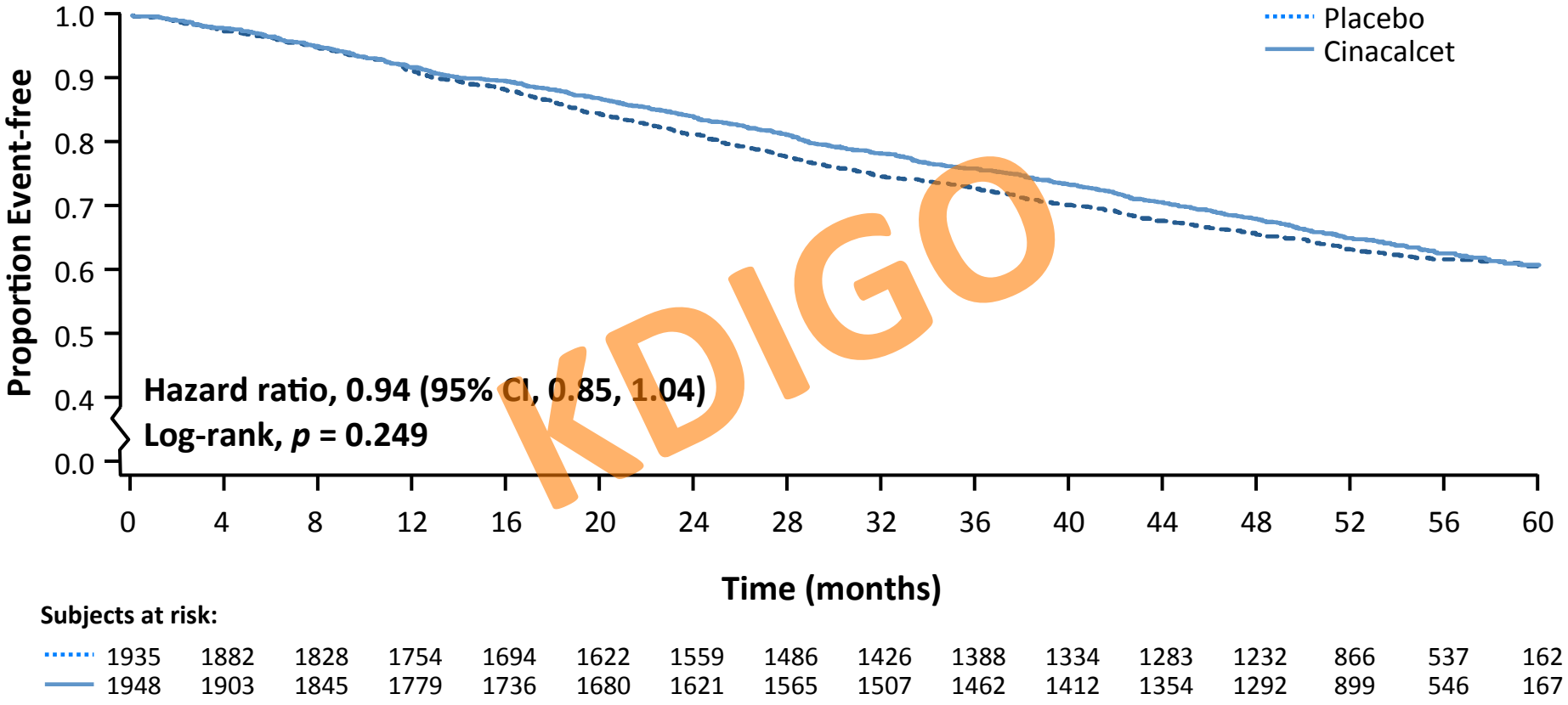

IV Paricalcitol-equivalent dose is calculated using the following: 2 mcg Paricalcitol (IV) = 1 mcg Doxercalciferol (IV) = 1 mcg Alfacalcidol (IV) = 0.5 mcg Calcitriol (IV) = 1 mcg Paricalcitol (PO) = 0.5 mcg Alfacalcidol (PO) = 0.25 mcg Calcitriol (PO)

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

# Kaplan-Meier Plot of Primary Composite Endpoint (ITT)



# Kaplan-Meier Plot of All-Cause Mortality (ITT)

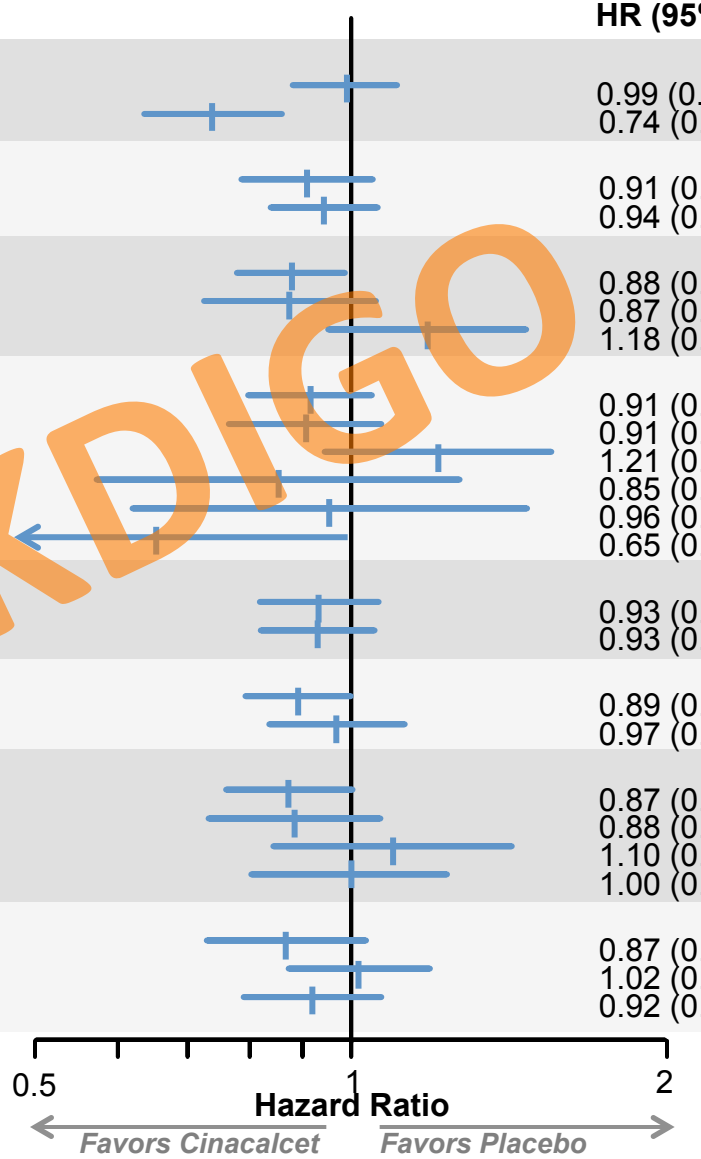


# Unadjusted and Adjusted ITT Analyses

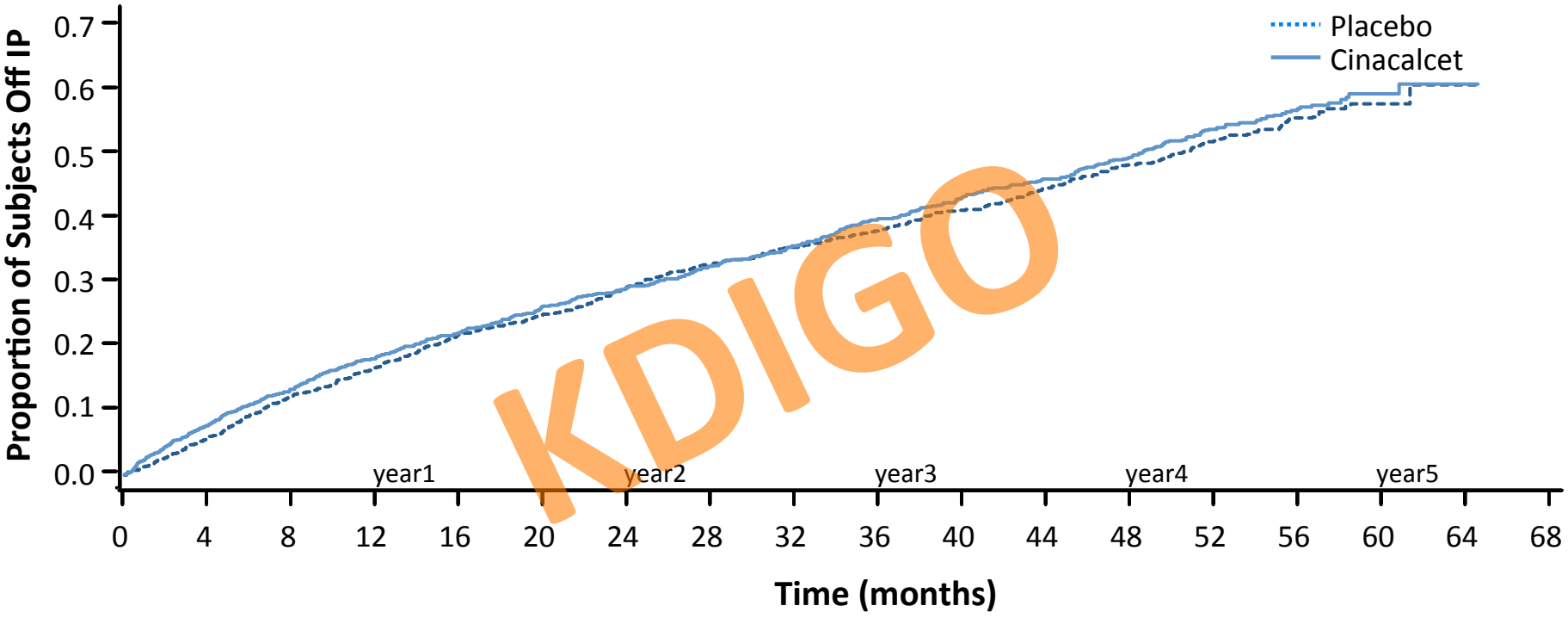
| Model | Relative Hazard | 95% CI | P-value |
|---|---|---|---|
| **Unadjusted** | 0.93 | 0.85 to 1.02 | 0.11 |
| **Age-adjusted** | 0.88 | 0.81 to 0.97 | 0.007 |
| **Multivariable (best fit)** | 0.88 | 0.79 to 0.97 | 0.008 |
| **Multivariable-adjusted (all included)** | 0.88 | 0.80 to 0.98 | 0.02 |

# Relative Hazards of Primary Composite Endpoint (ITT)

| Subgroup | N | HR (95% CI) | Interaction *p*-value |
|---|---|---|---|
| **Age** | | | 0.007 |
| < 65 yrs | 2878 | 0.99 (0.88, 1.11) | |
| ≥ 65 yrs | 1005 | 0.74 (0.63, 0.86) | |
| **Sex** | | | 0.784 |
| Female | 1578 | 0.91 (0.79, 1.05) | |
| Male | 2305 | 0.94 (0.84, 1.06) | |
| **Race Group** | | | 0.065 |
| White | 2240 | 0.88 (0.78, 0.99) | |
| Black | 837 | 0.87 (0.72, 1.06) | |
| Other | 806 | 1.18 (0.95, 1.47) | |
| **Region** | | | 0.165 |
| United States | 1430 | 0.91 (0.80, 1.05) | |
| Europe | 1188 | 0.91 (0.77, 1.07) | |
| Latin America | 687 | 1.21 (0.95, 1.56) | |
| Russia | 283 | 0.85 (0.57, 1.27) | |
| Canada | 146 | 0.96 (0.62, 1.48) | |
| Australia | 149 | 0.65 (0.43, 0.99) | |
| **Diabetes** | | | 0.943 |
| Yes | 1302 | 0.93 (0.82, 1.06) | |
| No | 2581 | 0.93 (0.82, 1.05) | |
| **BL Vitamin D** | | | 0.337 |
| Yes | 2310 | 0.89 (0.79, 1.00) | |
| No | 1573 | 0.97 (0.84, 1.13) | |
| **PTH Group** | | | 0.255 |
| 300-600 pg/mL | 1573 | 0.87 (0.76, 1.00) | |
| > 600-900 pg/mL | 929 | 0.88 (0.73, 1.07) | |
| > 900-1200 pg/mL | 550 | 1.10 (0.84, 1.43) | |
| >1200 pg/mL | 831 | 1.00 (0.80, 1.24) | |
| **Dialysis Vintage** | | | 0.432 |
| < 2 years | 1098 | 0.87 (0.73, 1.03) | |
| 2 to < 5 years | 1285 | 1.02 (0.87, 1.19) | |
| ≥ 5 years | 1499 | 0.92 (0.79, 1.07) | |



# Time to First Discontinuation of Study Drug due to Protocol-specified Reasons*



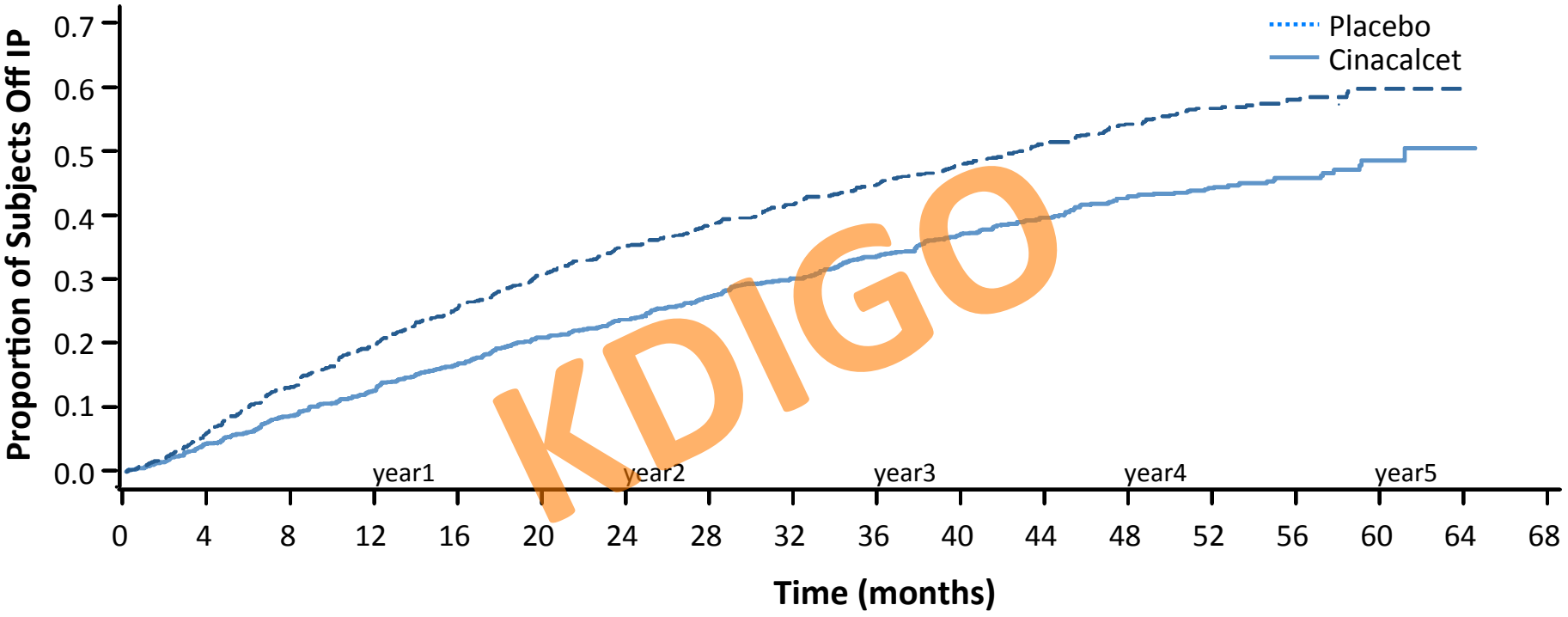



**Subjects at risk:**

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1938 | 1686 | 1491 | 1312 | 1180 | 1050 | 953 | 852 | 769 | 667 | 591 | 527 | 445 | 290 | 158 | 37 | 3 |
| 1923 | 1667 | 1419 | 1211 | 1033 | 897 | 777 | 675 | 595 | 530 | 461 | 396 | 336 | 205 | 105 | 30 | 2 |

*Safety Analysis Set

# Time to First Discontinuation from Study Drug due to Non-protocol Specified Reasons*






**Subjects at risk:**

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1938 | 1689 | 1499 | 1322 | 1191 | 1060 | 966 | 863 | 780 | 680 | 605 | 541 | 458 | 302 | 167 | 44 | 3 |
| 1923 | 1668 | 1421 | 1213 | 1033 | 900 | 787 | 688 | 609 | 543 | 476 | 409 | 351 | 218 | 115 | 35 | 2 |

*Safety Analysis Set

# Reasons for Discontinuation

| | Cinacalcet (N=1948) | Placebo (N=1935) |
|---|---|---|
| **Subjects who discontinued study drug (%)** | **66.7** | **70.5** |
| **Ineligibility determined** | 0.1 | 0.3 |
| **Consent withdrawn** | 1.8 | 2.2 |
| **Lost to follow-up** | 0.6 | 0.6 |
| **Adverse event** | **15.8** | 11.8 |
| **Protocol-specified reasons** | 22.1 | 20.1 |
| Parathyroidectomy | 2.4 | **7.6** |
| Kidney transplant | 13.3 | 11.9 |
| Calcium < 7.5 mg/dL or symptoms of hypocalcemia | **1.1** | 0.1 |
| Low PTH | **5.2** | 0.4 |
| Pregnancy | 0.0 | 0.1 |
| **Administrative decisions/subject request*** | 20.6 | **30.7** |
| Hyperparathyroidism | 1.9 | **6.5** |
| Commercial cinacalcet | 0.4 | **1.6** |
| Adverse event | **2.3** | 1.2 |
| Non-compliance | 3.5 | 3.3 |
| Other administrative decision/subject request | 12.9 | **19.7** |
| Commercial cinacalcet | 1.2 | **5.6** |
| **Other reasons** | 5.4 | 4.5 |
| **Missing reason** | 0.2 | 0.2 |
| **Never received study drug** | 0.5 | 0.6 |



N = Number of randomized patients. Percentages are based on N.

# Non-adherence to Study Drug

- Patients who prematurely stop study drug assume risk similar to the opposing group
  - "Drop-in": patients randomized to placebo who prematurely stop study drug and start commercial cinacalcet prior to primary endpoint
  - "Drop-out": patients randomized to cinacalcet who prematurely stop taking study drug prior to primary endpoint



| Total (N=3883) | n (%) | Observed Rates (%/yr) | Protocol Rates (%/yr) |
|---|---|---|---|
| Drop-in (Placebo) | 384 (20%) | 7.4 | 10.0 |
| Drop-out (Cinacalcet) | 1207 (62%) | 27.3 | 10.0 |

# Intention-to-Treat (ITT)

- 3 principles of ITT*:
  1. Use all randomized patients
  2. Use original randomization allocation, regardless of adherence to study drug
  3. Measure outcome data on all patients
- "Gold standard" to assess the effectiveness of a study drug in randomized clinical trials
  - Provides unbiased comparisons between the 2 groups
    - Known or unknown prognostic factors of the outcome should be balanced when randomization is preserved



*Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

# Time off Study Drug *versus* Time on Study

| Months | Cinacalcet (N=1948) | Placebo (N=1935) |
|---|---|---|
| Time on study Median (Q1, Q3) | 50.6 (31.3, 56.4) | 50.4 (26.7, 56.4) |
| Time on study drug Median (Q1, Q3) | 21.2 (8.1, 40.8) | 17.5 (7.1, 37.9) |



Time on study drug was less than half of the time patients were on study

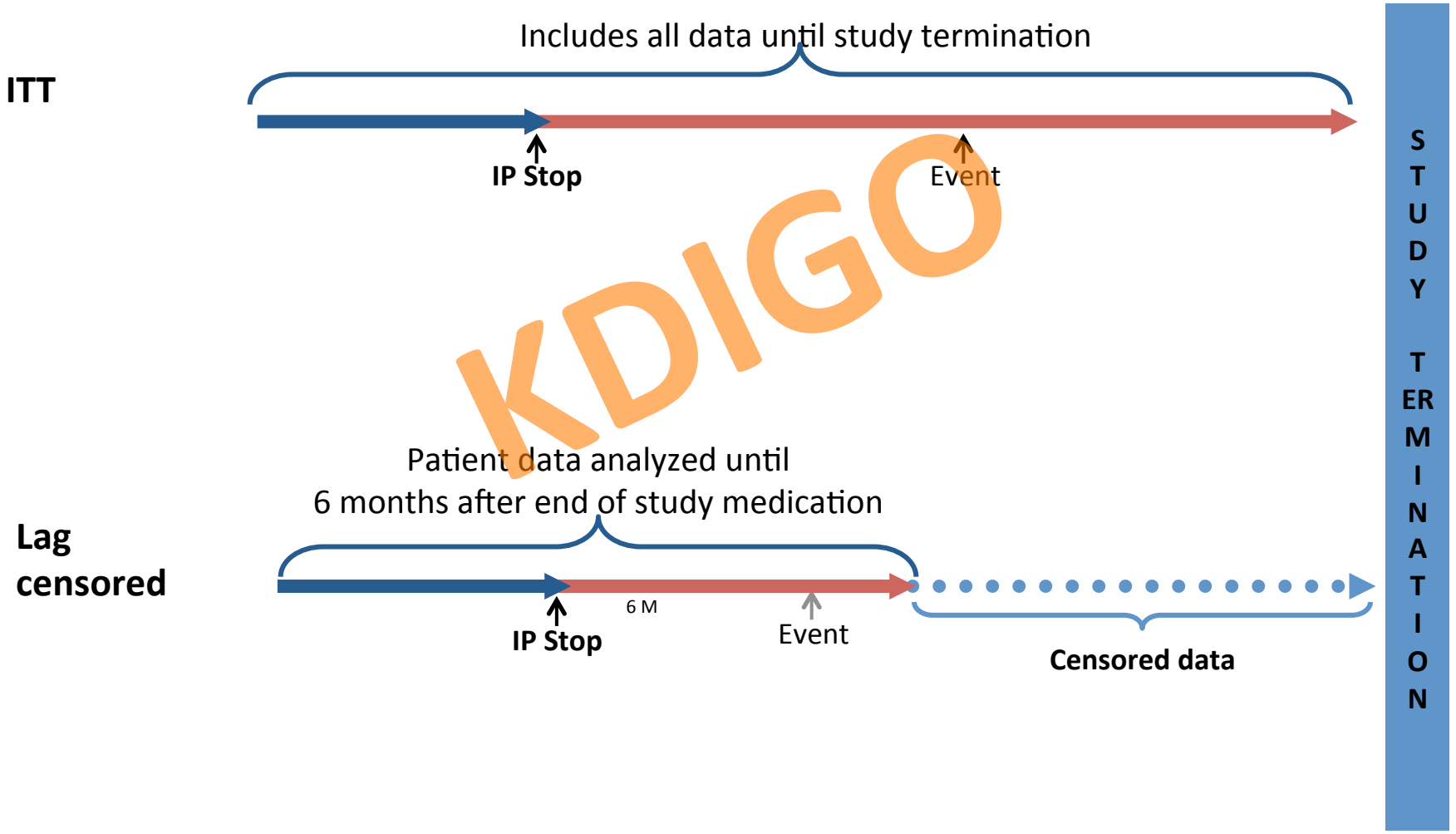
# Considering Non-adherence

- We anticipated non-adherence to study drug
- We pre-specified lag censoring analysis (6 months) in the Statistical Analysis Plan
- We pre-specified two additional approaches in the Supplemental SAP
  - Iterative Parameter Estimation (IPE)
  - Inverse Probability Censoring Weight (IPCW)

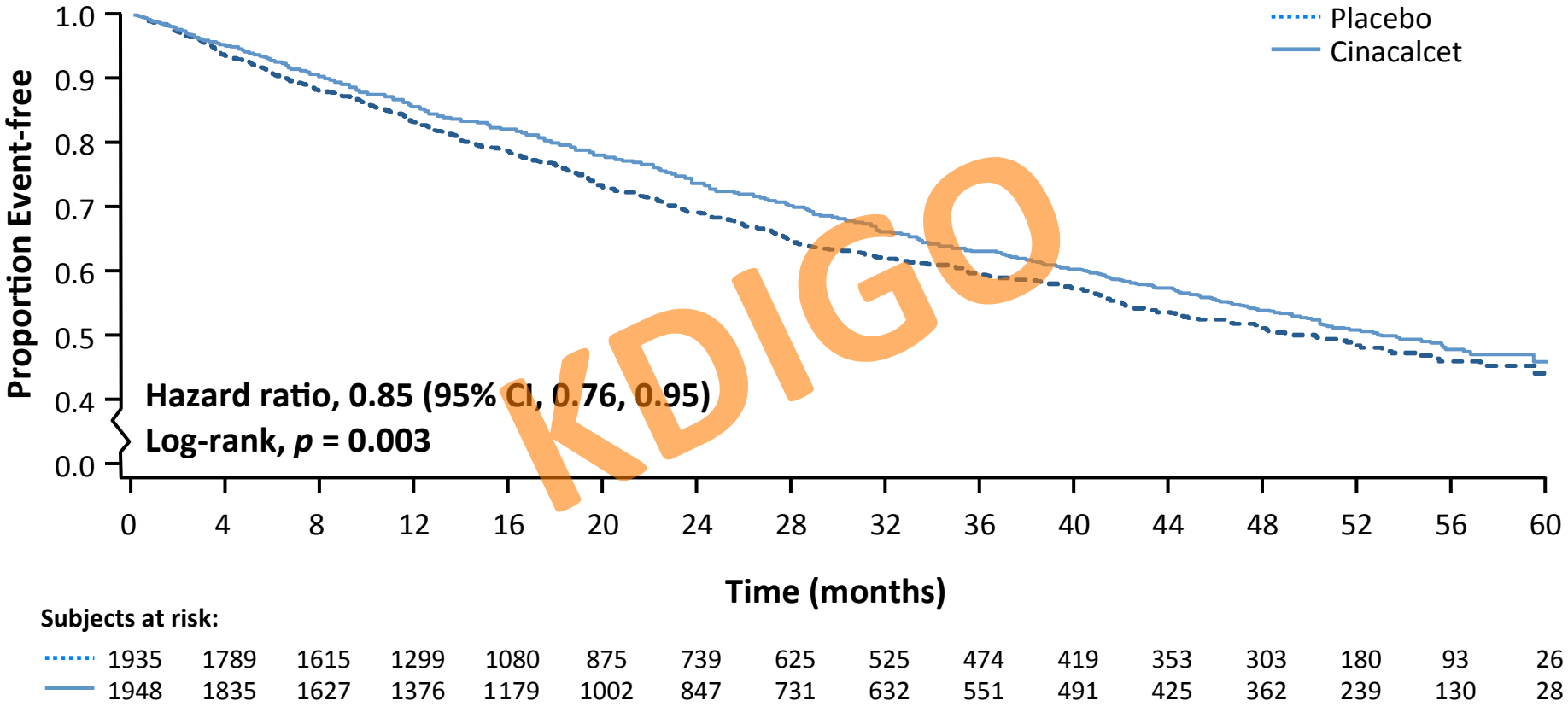
# Lag Censoring Analysis

- Censors data at a timepoint when the treatment effect was thought to be diminished
  - Requires clinical judgement
- Preserves randomization

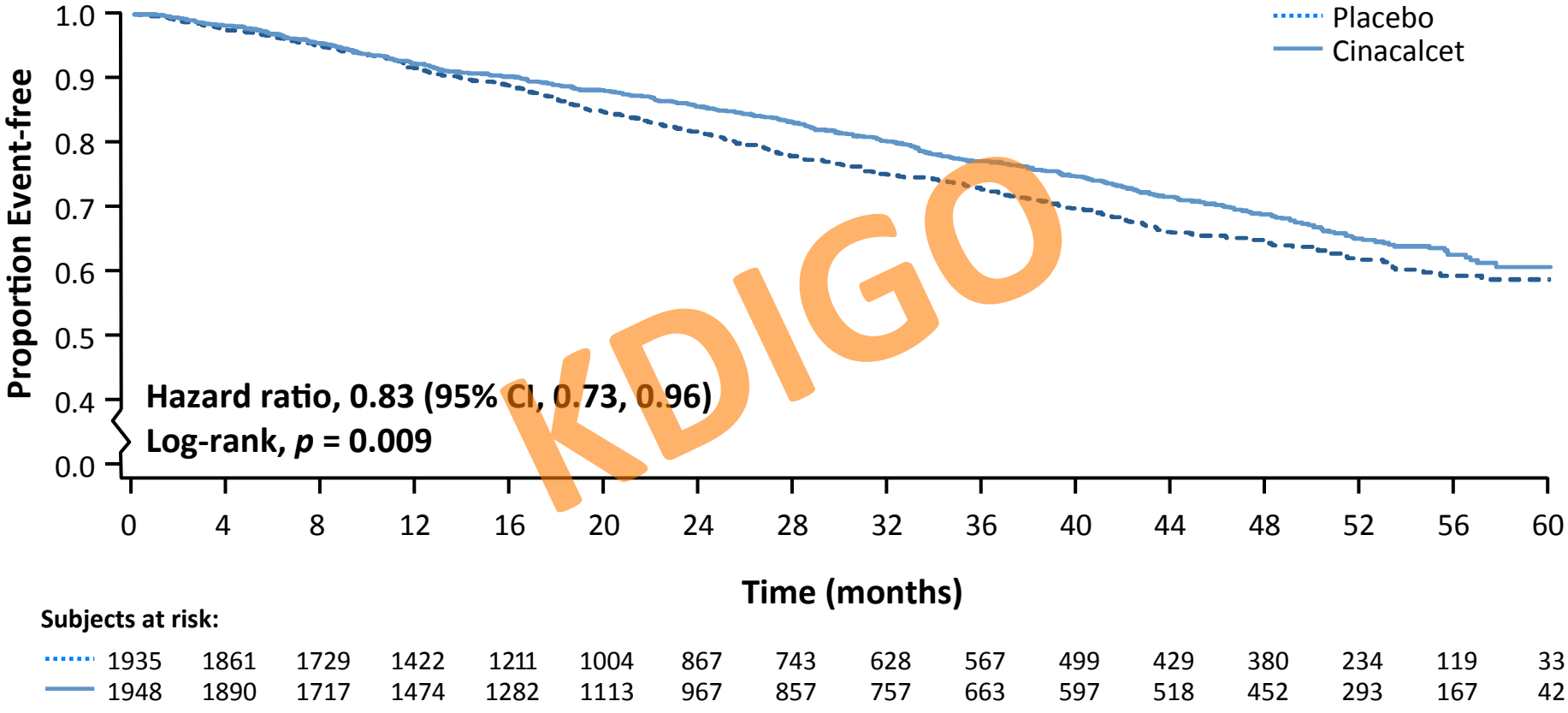
# ITT *versus* Lag Censored Analysis



# Kaplan-Meier Plot of Primary Composite Endpoint (Lag Censoring)



# Kaplan-Meier Plot of Mortality (Lag Censoring Analysis)



# Lag Censoring Analysis PROs/CONs

| PROs |
| --- |
| Preserves randomization |
| Simple to use and easy to understand |

| CONs |
| --- |
| Assumes stopping study drug is random between the 2 treatment groups<br>Prone to bias since patients who are non-adherent may have different prognostic characteristics and may be more/less likely to experience an event than those who did not (informative censoring) |
| Violates ITT principle:<br>Does not include all follow-up information |

# Iterative Parameter Estimation (IPE)

- Based on accelerated failure time model
  - Treatment effect on survival time is modeled through a multiplicative factor ($exp^{-n}$)

$$T_{calci} = exp^{-n} T_{placebo} \quad (1)$$

$T_{calci}$ = survival time of cinacalcet patients who remained on study drug

$T_{placebo}$ = survival time of placebo patients who are not receiving commercial cinacalcet

- Models survival time as if dropin patients never started commercial cinacalcet and dropout patients remained on study drug
  - Using algorithm 1, the survival time is contracted for dropin patients and expanded for dropout patients
  - Survival times are transformed through iterative process until the model converges

# IPE PROs/CONs

| PROs | CONs |
| --- | --- |
| Preserves randomization | Requires parametric modeling, need to specify correct distribution. Results may be sensitive to selected distribution. |
| No need to model the pattern when patients dropin/dropout | Required to re-censor data when the transformed survival time is beyond the study termination date |
| Simple to use and relatively easy to understand | Assumes non-adherence is random (not related to prognostic factors of the outcome) |
| | Computational methods such as bootstrapping are required to obtain robust confidence intervals |

# Inverse Probability of Censoring Weight (IPCW)

- IPCW method censors data when non-adherence occurs (ie, weight=0 for time periods after this timepoint)
- For patients who were adherent and had similar characteristics to those who were not, IPCW method assigns bigger weights to these patients to "re-create" the population that would have been observed
- Weights are calculated based on the inverse of the probability that patients remains adherent using a logistic regression model
- Final hazard ratio is derived from a weighted Cox regression model

# IPCW (cont'd)

- In EVOLVE, demographics, adverse events and lab assessments were used to estimate the probability of adherence
  - Age
  - Sex
  - Race group
  - Country
  - History of diabetes
  - Randomized treatment group
  - Time dependent covariates of PTH, adverse events of hypocalcemia, nausea or vomiting

# IPCW PROs/CONs

| PROs | CONs |
| --- | --- |
| Preserves randomization | Difficult model specification; must have no unknown confounders for adherence<br>Missing data may cause biased weights |
| Takes into account informative censoring | Computationally difficult to implement: creation of dataset is difficult; parameter estimates may not be stable since model may not converge |
| Adjusts for time dependent confounders | Sensitive to amount of non-adherent patients, results may be biased or unstable |

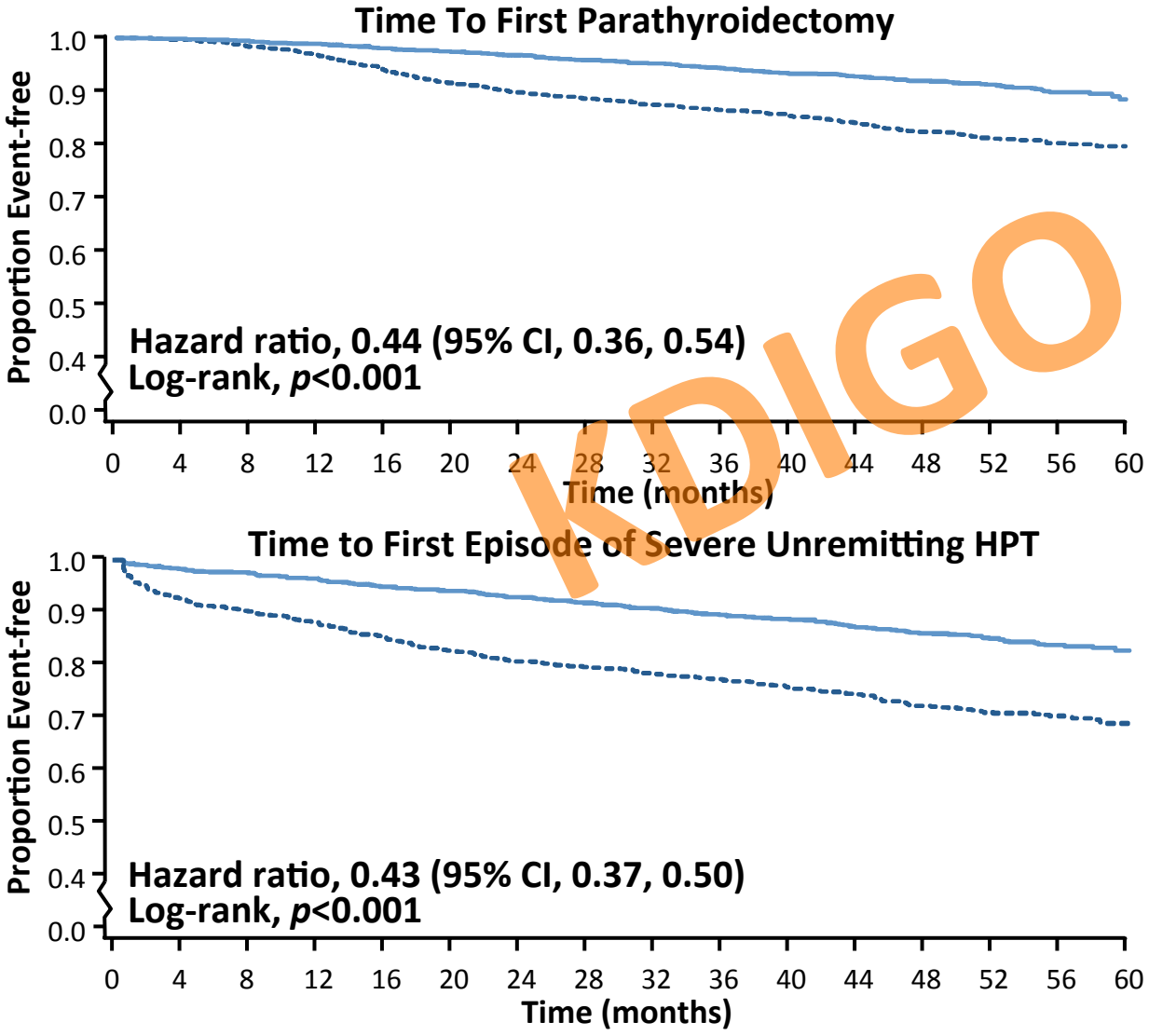
# Results – Primary Composite Endpoint

| Method | Hazard Ratio | 95% CI | p-value |
|---|---|---|---|
| ITT | 0.93 | (0.85, 1.02) | 0.112 |
| Lag censoring | 0.85 | (0.76, 0.95) | 0.003 |
| IPE | 0.87 | (0.75, 1.02) | 0.081 |
| IPCW | 0.77 | (0.66, 0.88) | <0.001 |

# Primary Composite Endpoint: Sensitivity Analyses

| Analysis Type | Placebo (N=1935) | Cinacalcet (N=1948) | HR (95% CI) | p-value |
|---|---|---|---|---|
| ITT | 952 (49.2) | 938 (48.2) | 0.93 (0.85, 1.02) | 0.112 |
| Lag Censoring (6 mos) | 658 (34.0) | 638 (32.8) | 0.85 (0.76, 0.95) | 0.003 |
| Censor at PTX | 911 (47.1) | 916 (47.0) | 0.90 (0.82, 0.99) | 0.031 |
| Censor at KTX | 907 (46.9) | 891 (45.7) | 0.90 (0.82, 0.99) | 0.029 |
| Censor at Commercial Cinacalcet Use | 818 (42.3) | 870 (44.7) | 0.90 (0.82, 0.99) | 0.032 |
| Censor at PTX or Commercial Cinacalcet Use | 786 (40.6) | 854 (43.8) | 0.87 (0.79, 0.96) | 0.006 |
| Censor at PTX, Commercial Cinacalcet, or KTX | 748 (38.7) | 812 (41.7) | 0.84 (0.76, 0.93) | <0.001 |

# Kaplan-Meier Plots for Time to First Parathyroidectomy or Time to First Episode of Severe Unremitting HPT (ITT)

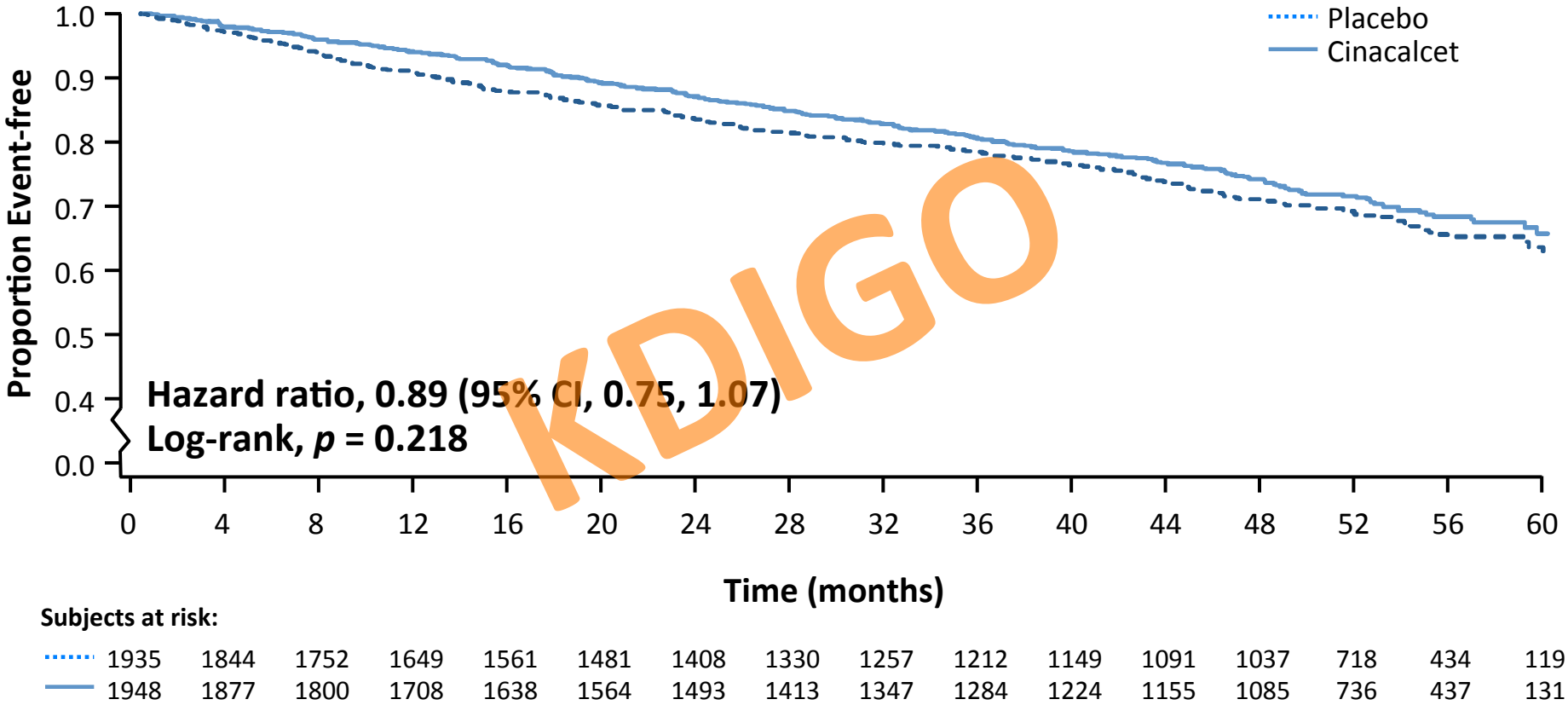





**Severe, unremitting HPT**

- 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

# Kaplan-Meier Plots for Time to First Clinical Fracture (ITT)






N = Number of patients in the intent-to-treat analysis set; n = Number of patients with laboratory value at the study visit

# 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



*p<0.001

# Conclusions

- Cinacalcet significantly reduces rates of parathyroidectomy and severe, unremitting hyperparathyroidism
- Using an unadjusted intent-to-treat approach, there was a 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
- After adjusting for age, or for age + other characteristics, there was a nominally significant 12% reduction in the risk of death or major cardiovascular events
- With lag censoring, effects were more pronounced
- Any potential benefits must be balanced against risks and discomforts

# Key Discussion Points

- Conducting clinical trials of approved drugs
- Conflicting roles of clinical practice guidelines
- Effects of co-interventions
- Unadjusted or adjusted primary analysis
- Analytic approaches in clinical trials with reduced adherence