Cardiovascular Events in Secondary Hyperparathyroidism

- Lessons learned from the EVOLVE study

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Views expressed are those of the speaker not necessarily those of Amgen

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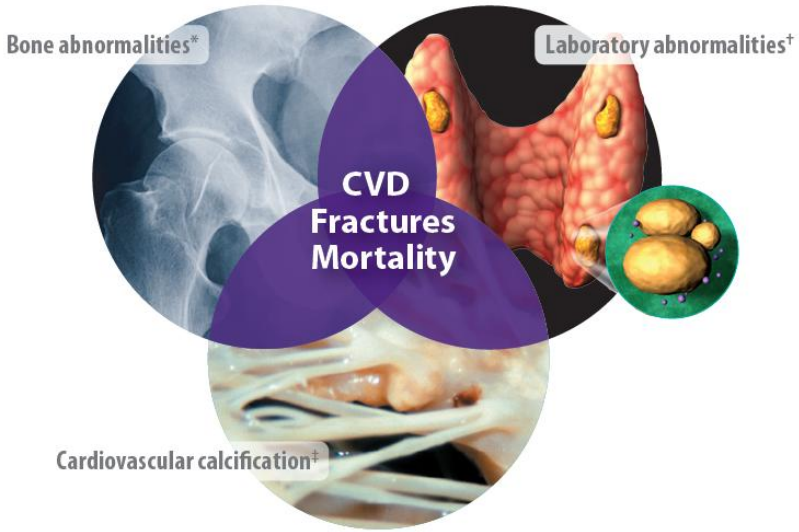
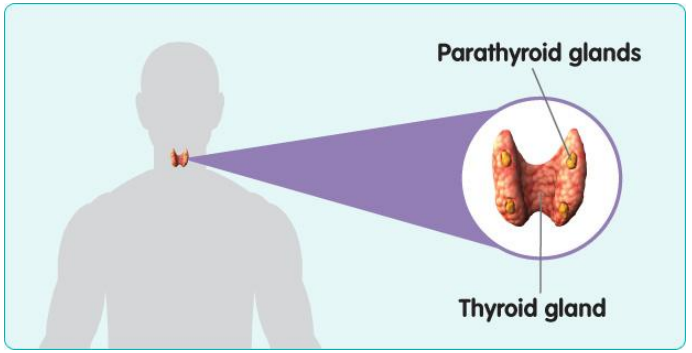
Background

Cinacalcet (Mimpara/Sensipar)

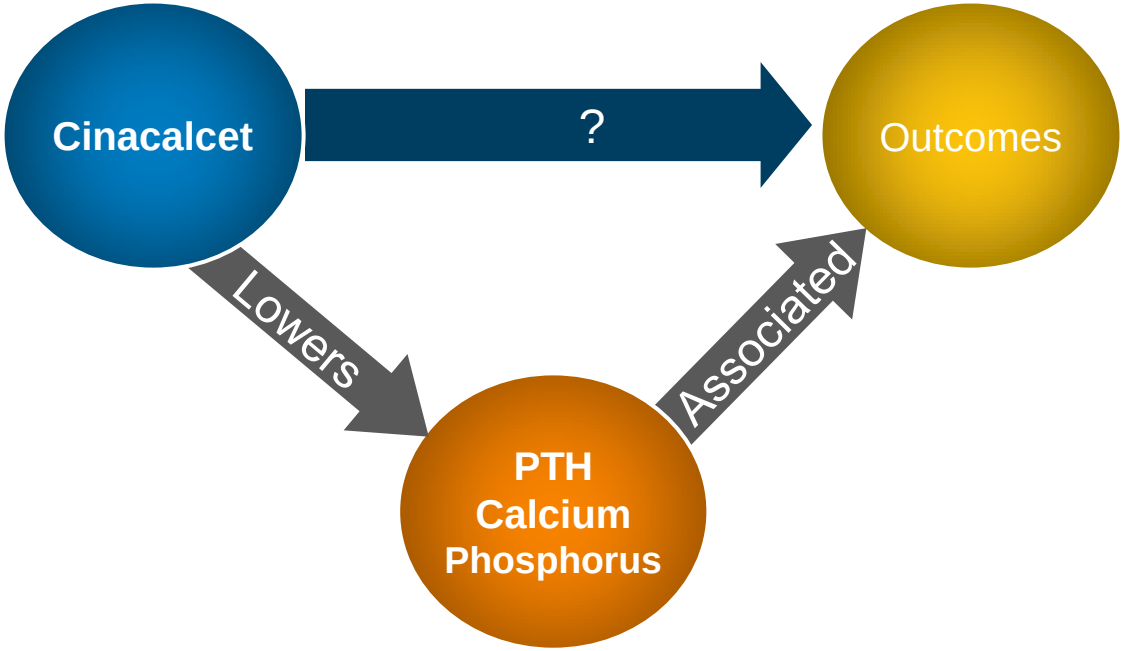
- Licensed indications include treatment of secondary hyperparathyrodism (sHPT) in patients with chronic kidney disease on dialysis
- Reduces parathyroid hormone levels (PTH), calcium and phosphorus
- Pill, taken daily. Titratable drug.



Chronic kidney disease - bone and mineral disorder



EVOLVE Hypothesis

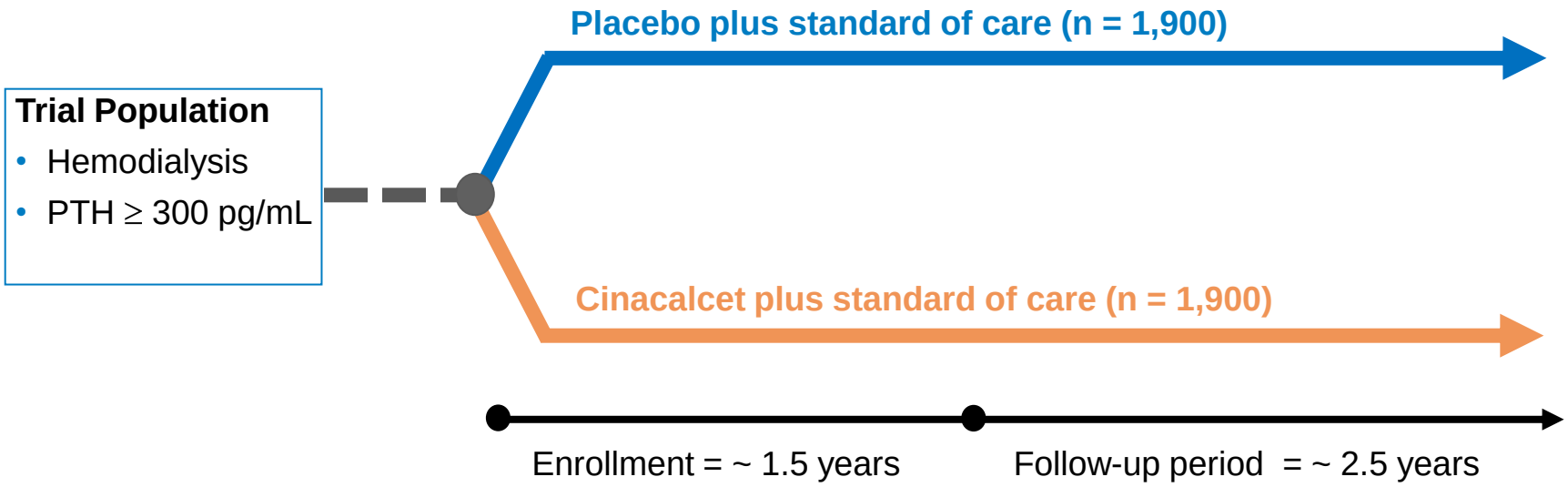


A treatment regimen for secondary hyperparathyroidism (HPT) including cinacalcet reduces the risk of mortality and cardiovascular morbidity compared to a treatment regimen without cinacalcet in subjects with chronic kidney disease (CKD) receiving maintenance hemodialysis

Study Design

Global, randomised (1:1), double-blind, placebo-controlled study

Randomisation stratified by history of diabetes and country



Primary Endpoint
Time to composite event:
- Mortality
- Myocardial infarction
- Hospitalisation for unstable angina
- Heart failure
- Peripheral vascular event

Secondary Endpoints:
Time to:
- Cardiovascular mortality
- Stroke
- Parathyroidectomy
- Clinical bone fracture
- Individual elements of composite

Sample Size

- Study was designed to have 90% power to detect a 20% risk reduction for the primary endpoint (HR of 0.80)
- Assumptions:
  - Overall α = 0.05
  - Placebo event rate: 23% per year
  - Loss to follow up rate: 1% per year
  - Drop-out rate: 10% per year
    - **Drop-out: subject who is randomised to cinacalcet withdraws from cinacalcet before experiencing a primary event**
  - Drop-in rate: 10% per year
    - **Drop-in: subject who is randomised to placebo starts commercial cinacalcet treatment before experiencing a primary event**
  - Study duration of 4 years

➡ 1882 subjects to experience a primary composite event
(3800 to be randomised)

Effect of Drop-in and Drop-out on Observed Treatment Effect

- Assuming true HR of 0.80
  - With planned drop-in and drop-out rates, observed HR estimated to be 0.86-0.87
- Observed treatment effect will be diluted

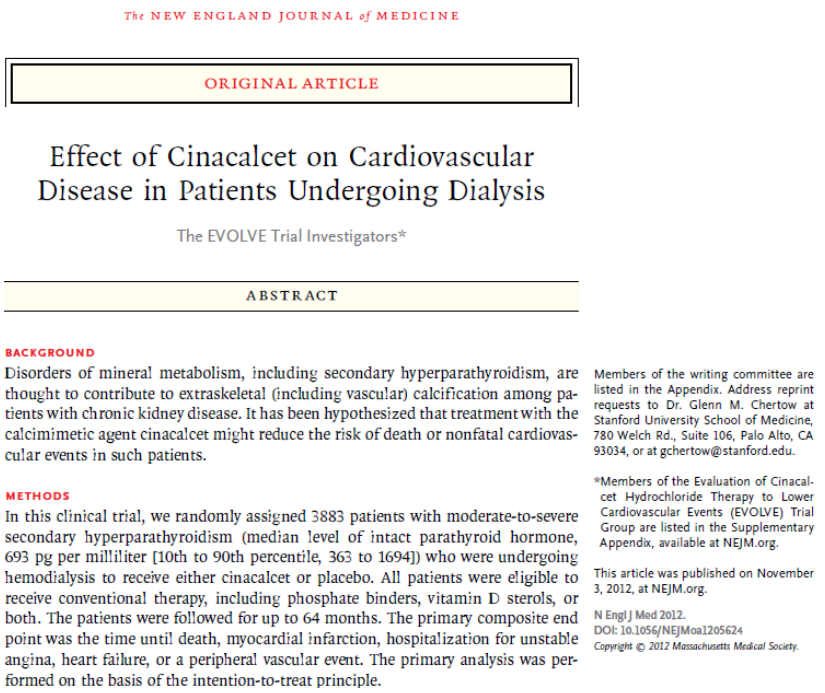
Results

Publication of Results

- Press Release, June 2012

  'Although patients in the Sensipar®/Mimpara® arm experienced numerically fewer composite primary events, the results were not statistically significant, and the trial did not meet its primary endpoint in the intent-to-treat analysis'

- Manuscript NEJM, Nov 2012



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Cinacalcet on Cardiovascular Disease in Patients Undergoing Dialysis

The EVOLVE Trial Investigators*

ABSTRACT

BACKGROUND

Disorders of mineral metabolism, including secondary hyperparathyroidism, are thought to contribute to extraskeletal (including vascular) calcification among patients with chronic kidney disease. It has been hypothesized that treatment with the calcimimetic agent cinacalcet might reduce the risk of death or nonfatal cardiovascular events in such patients.

METHODS

In this clinical trial, we randomly assigned 3883 patients with moderate-to-severe secondary hyperparathyroidism (median level of intact parathyroid hormone, 693 pg per milliliter [10th to 90th percentile, 363 to 1694]) who were undergoing hemodialysis to receive either cinacalcet or placebo. All patients were eligible to receive conventional therapy, including phosphate binders, vitamin D sterols, or both. The patients were followed for up to 64 months. The primary composite end point was the time until death, myocardial infarction, hospitalization for unstable angina, heart failure, or a peripheral vascular event. The primary analysis was performed on the basis of the intention-to-treat principle.

Members of the writing committee are listed in the Appendix. Address reprint requests to Dr. Glenn M. Chertow at Stanford University School of Medicine, 780 Welch Rd., Suite 106, Palo Alto, CA 93034, or at gchertow@stanford.edu.

*Members of the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) Trial Group are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on November 3, 2012, at NEJM.org.

N Engl J Med 2012.
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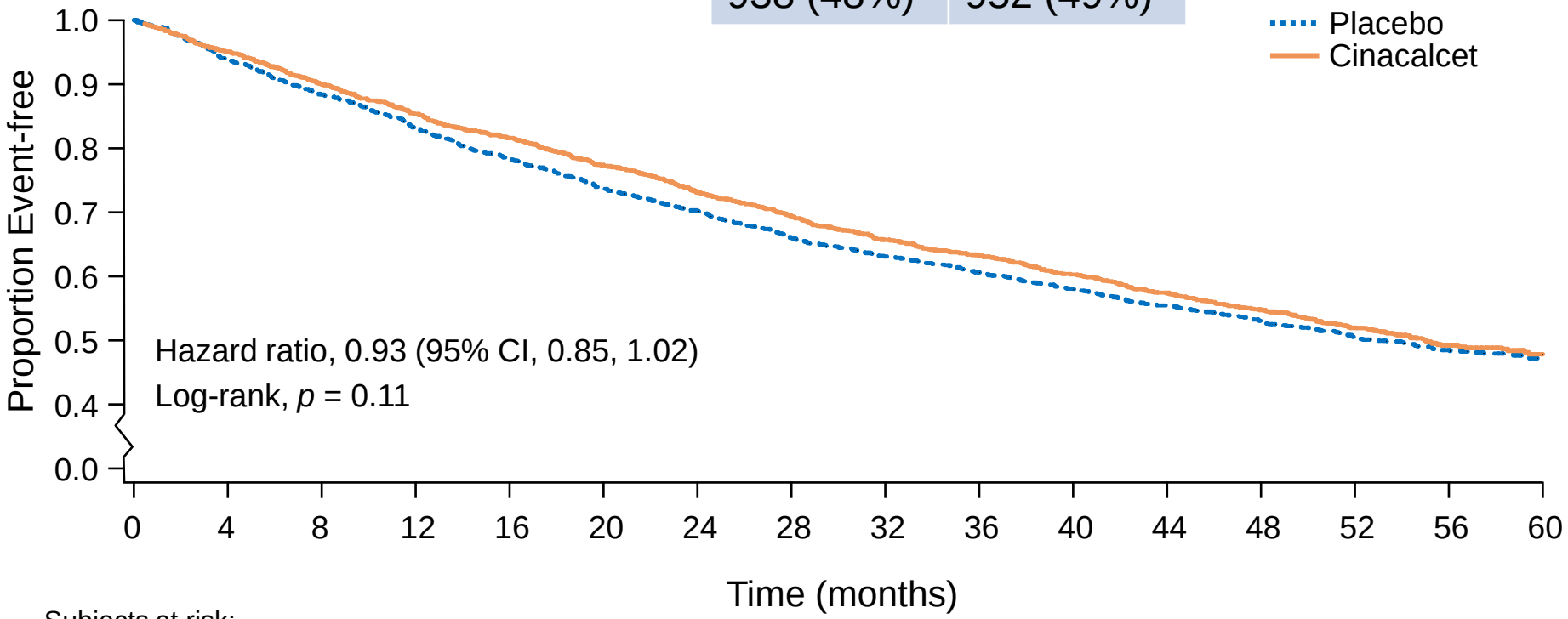
Primary Endpoint Result (Primary ITT analysis)

Cinacalcet (N=1948)	Placebo (N=1935)
938 (48%)	952 (49%)



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

Study Issues

Issue 1- Baseline Imbalance

- 1 year difference in median age at baseline despite enrolling almost 4000 subjects

Age (Years)	Cinacalcet (n = 1,948)	Placebo (n = 1,935)
Mean	54.8	54.0
SD	14.5	14.2
Median	55.0	54.0
Percentiles (10, 90)	35.0, 74.0	35.0, 73.0
Min, Max	18, 91	18, 92

- HR (95% CI) for age on the primary endpoint was 1.032 (1.028, 1.037) per 1 year increase in age

Adjusted vs Unadjusted Analysis

Analysis	HR	95% CI	p-value
Unadjusted* ***Pre-specified primary analysis***	0.93	0.85 to 1.02	0.11
Age-adjusted	0.88	0.81 to 0.97	0.007
Multivariate (best fit)	0.88	0.79 to 0.97	0.008
Multivariate (all 40 covariates included)	0.88	0.80 to 0.98	0.02

*stratified by randomisation factors (history of diabetes and country)

p-values are nominal except for primary analysis

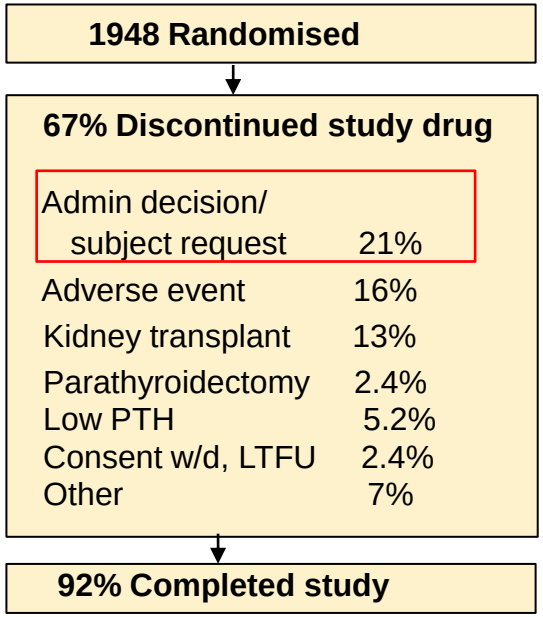
Probability of Age Imbalance

- ~8% chance of difference in mean age ≥ 0.8 yrs
  - Standard deviation (SD) for age and sample size dictates likelihood of imbalance
  - SD larger in sHPT population than other CV trials

Age SD	Probability of |Age Diff| ≥ 0.8 Yrs	Example Trial Populations (assume N's in EVOLVE)
20	0.20	
14	0.08	EVOLVE, HEMO, Cinacalcet Ph3, DCOR
12	0.04	SHARP
11	0.02	CHARM, MIRACLE, PRAISE, RED-HF
10	0.01	TREAT
8	0	4D, AURORA

Issue 2 - Adherence to Randomised Treatment

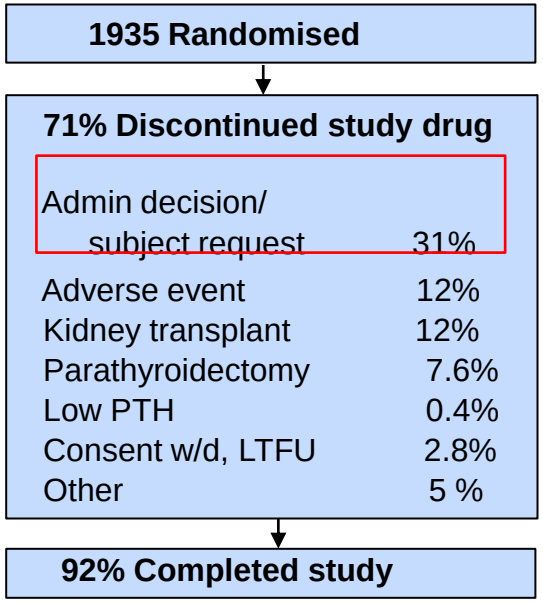
Cinacalcet



Median time on treatment: 21.2 months
Median time on study: 50.4 months

11% started commercial cinacalcet

Placebo



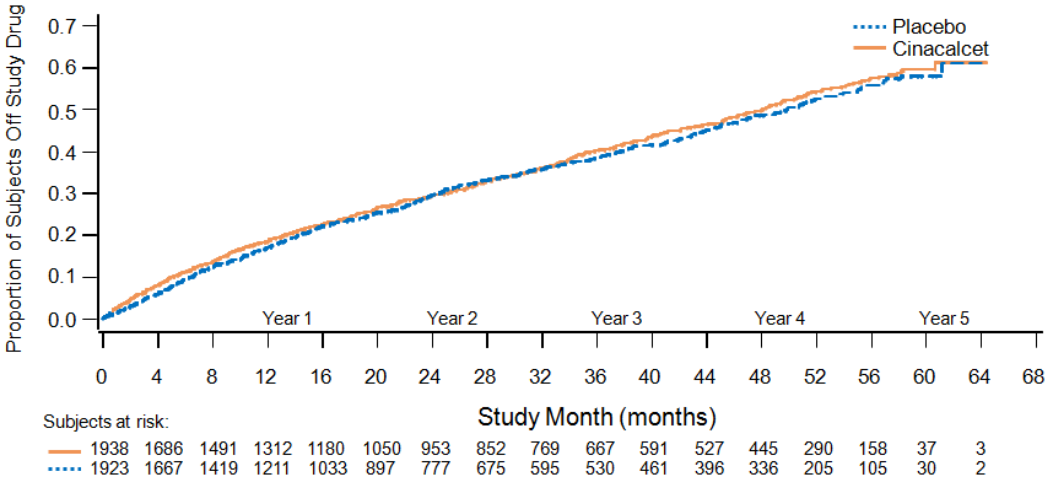
Median time on treatment : 17.5 months
Median time on study : 50.4 months

22% started commercial cinacalcet

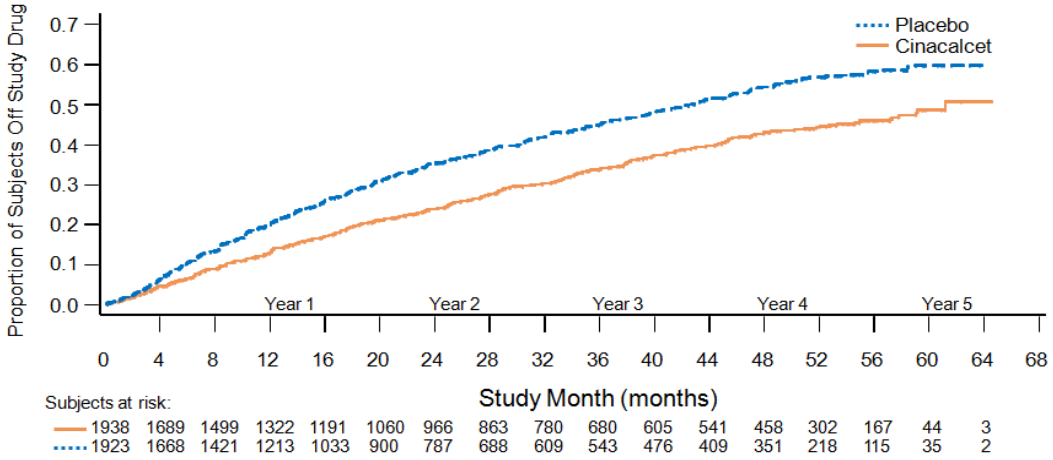
LTFU = lost to follow-up

Time to Discontinuation from Study Drug

1. For protocol specified reasons e.g. kidney transplant, parathyroidectomy, low PTH



2. For non-protocol specified reasons e.g. administrative decision, subject request



Drop-in and Drop-out

Total (N=3883)	n/N (%)	Mean (SD) Time to Drop-in/Out (month)	Observed Rates (%/yr)	Protocol Assumed Rates (%/yr)
Drop-in (Placebo)	384/1935 (20%)	17.3 (13.1)	7.4	10
Drop-out (Cinacalcet)	1207/1948 (62%)	18.0 (15.2)	27.3	10

Drop-in: subjects randomised to placebo who start commercial cinacalcet prior to having an event

Drop-out: subjects randomised to cinacalcet who withdraw from cinacalcet (study drug or commercial cinacalcet) prior to having an event

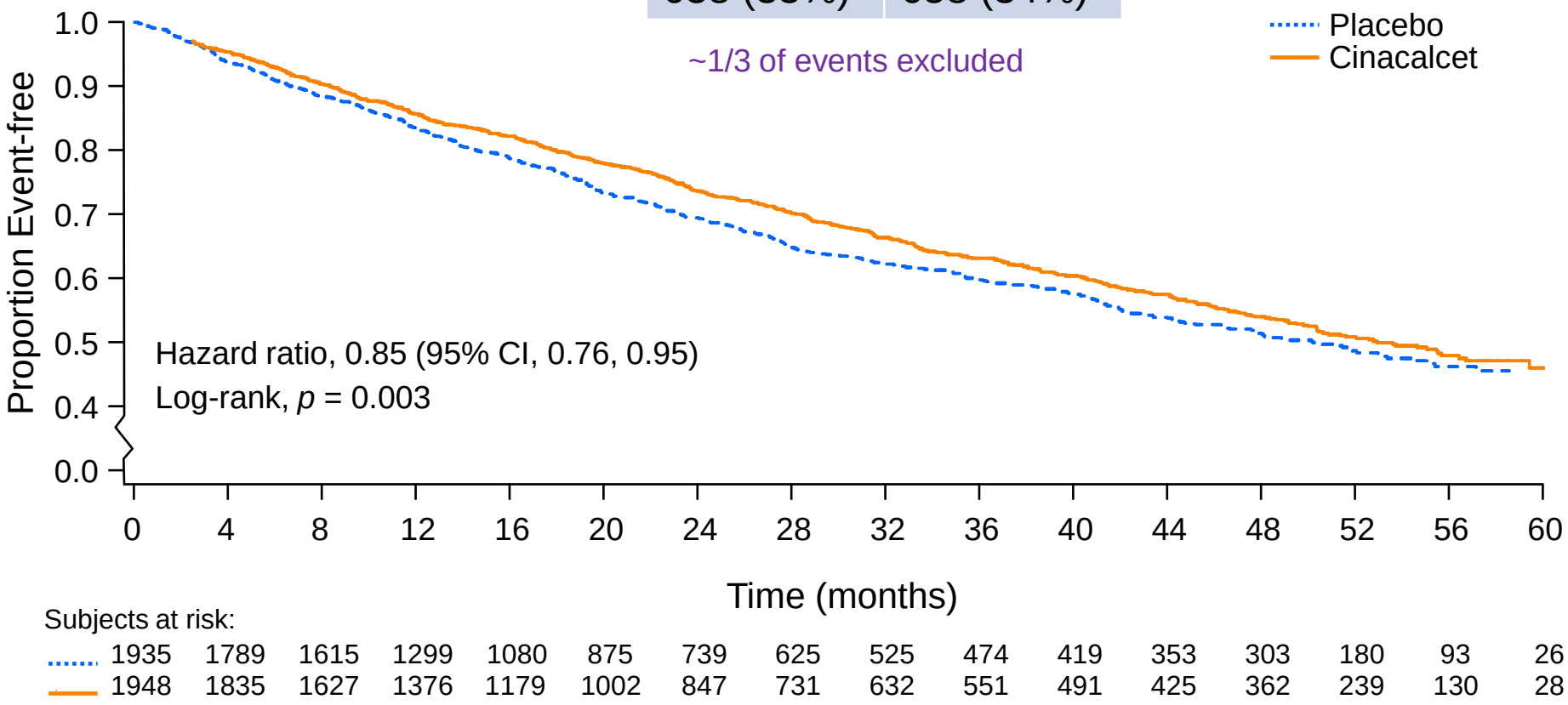
Sensitivity Analyses Addressing Treatment Adherence

- Lag censoring analysis
  - Censors data 6 months after stopping study drug
  - Other lag times explored (0-18 months)
- Censoring at time of commercial cinacalcet use
- Inverse probability of censoring weights (IPCW)

Lag Censoring Analysis
(Censoring 6 months after stopping study drug)

Cinacalcet (N=1948)	Placebo (N=1935)
638 (33%)	658 (34%)

~1/3 of events excluded



Subjects at risk:

1935	1789	1615	1299	1080	875	739	625	525	474	419	353	303	180	93	26
1948	1835	1627	1376	1179	1002	847	731	632	551	491	425	362	239	130	28

p-value is nominal

Effect of Varying the Lag Time

Table S7: Effect of lag durations on primary composite endpoint using lag-censoring analysis

Lag Duration (months)	Cinacalcet (N=1948)	Placebo (N=1935)	Hazard Ratio (95% CI)	p-value
0	423 (21.7)	463 (23.9)	0.79 (0.69, 0.91)	<0.001
3	594 (30.5)	616 (31.8)	0.83 (0.74, 0.93)	0.002
6	638 (32.8)	658 (34.0)	0.85 (0.76, 0.95)	0.003
9	672 (34.5)	692 (35.8)	0.86 (0.77, 0.96)	0.005
12	705 (36.2)	722 (37.3)	0.87 (0.78, 0.96)	0.008
18	772 (39.6)	768 (39.7)	0.91 (0.82, 1.00)	0.054

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

p-values are nominal

Censoring at Commercial Cinacalcet Use

- Commercial cinacalcet initiated in 11% of cinacalcet arm and 22% of placebo arm

Censor Point	Cinacalcet (N=1948) n (%)	Placebo (N=1935) n (%)	HR (95%CI)	p-value
Commercial cinacalcet	870 (45)	818 (42)	0.90 (0.82, 0.99)	0.03

p-value is nominal

Informative Censoring

- Censoring in survival analysis should be non-informative
- ITT analysis – censor only where necessary
  - consent withdrawn, loss to follow up or end of study date
- Lag censoring analysis and analysis censoring at commercial cinacalcet start are subject to bias
- Inverse Probability of Censoring Weights (IPCW) analysis performed to address this
  - Robins and Finkelstein (2000)
  - Has been used in many large long-term clinical trials
  - Accepted by NICE
  - The covariates of censored subjects are taken into account in an attempt to remove bias

Inverse Probability of Censoring Weights (IPCW)

- Method
  - Partition follow-up time into intervals
  - Censor at time of treatment discontinuation
  - Model the probability of remaining on treatment at the end of each interval
    - Include all covariates that predict treatment adherence and outcome
  - Adherent subjects are then weighted by the inverse of that probability in the final analysis
- Result
  - HR 0.77 (95% CI 0.66 to 0.88)
- 'No unmeasured confounders' assumption
  - requires data on all covariates (baseline and time-dependent) that may influence treatment discontinuation

Other Methods for Addressing Treatment Adherence

Methods based on accelerated failure time models being explored

- Rank Preserving Structural Failure Time Models (RPSFTM)
  - Robins and Tsiatis, 1991
- Iterative Parameter Estimation (IPE)
  - Branson and Whitehead, 2002
  - Extension of RPSFTM using parametric failure time model

Issue 3 - Surgical Procedures that Modify Risk of Event

- Parathyroidectomy
  - Occurred in 7% of cinacalcet arm and 14% of placebo arm
  - Time to parathyroidectomy HR 0.44, 95% CI 0.36 to 0.54
- Kidney transplant
  - Occurred in 18% of cinacalcet arm and 19% of placebo arm

- Primary endpoint results from analyses censoring at time of procedure:

Censor Point	Cinacalcet (N=1948) n (%)	Placebo (N=1935) n (%)	HR (95%CI)	p-value
Parathyroidectomy	916 (47)	911 (47)	0.90 (0.82, 0.99)	0.03
Kidney transplant	891 (46)	907 (47)	0.90 (0.82, 0.99)	0.03

p-values are nominal

Issue 4 – Low Event Rate

- Pooled composite event rate assessed after 90% subjects randomised
  - Lower than expected
  - Option to extend trial duration or enrol more subjects
  - Decision to extend duration by 1.4 years to 5.5 years
    - Magnifies impact of drop-in/drop-out
- Assumed placebo event rate: 23 % per year
- Actual placebo event rate varied by region
  - Ranged from 24% per year (Australia) to 9% per year (Latin America and Russia)

Summary and Lessons Learned

Summary of Results

	HR (95% CI)	p-value
Primary ITT Analysis	0.93 (0.85, 1.02)	0.11
Adjusted ITT Analysis	0.88 (0.79, 0.97)	0.008
Sensitivity Analyses		
Lag censoring (6 mths)	0.85 (0.76, 0.95)	0.003
Censor at parathyroidectomy (PTx)	0.90 (0.82, 0.99)	0.03
Censor at kidney transplant (KTx)	0.90 (0.82, 0.99)	0.03
Censor at commercial cinacalcet	0.90 (0.82, 0.99)	0.03
Censor at PTx, KTx or commercial cinacalcet	0.84 (076, 0.93)	<0.001
IPCW	0.77 (0.66, 0.88)	

p-values are nominal except for primary analysis

Summary of Issues

- Unanticipated baseline imbalance on important prognostic variable of the outcome
- Commercial availability of study drug
  - Placebo arm drop-in
- High drop-out rate in cinacalcet arm
- Availability of surgical curative procedures
  - Higher rate of parathyroidectomy in placebo arm
- Lower than expected event rate
  - Trial duration extended
  - Impact on drop-in/drop-out

Power 

Lessons Learned

- Consider an adjusted analysis as primary if there are known key prognostic factors of the outcome
  - be aware of the distribution of such factors and how that may affect the risk of observing baseline imbalance
- Start outcome trials as early as possible
  - before drug commercially available
- Consider impact of
  - less subjects + longer trial vs more subjects + shorter trial
- When designing study in new regions, explore characteristics of patient population and potential effect on event rate