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Lessons Learned from Recent Trials: Case Studies

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Disclosure

- Employee of Amgen; stock ownership in Amgen
- The views expressed in this presentation are my own and do not necessarily represent the views or practices of Amgen or any other party

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Topics to Address Today

- Why do we design trials the way we do
- EVOLVE as a case study
- REVOLVE as a potential LST
- Areas of opportunity

The NEW ENGLAND JOURNAL of MEDICINE

A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease

Marc A. Pfeffer, M.D., Ph.D., Emmanuel A. Burdmann, M.D., Ph.D., Chao-Yin Chen, Ph.D., Mark E. Cooper, M.D., Dick de Zeeuw, M.D., Ph.D., Kai-Uwe Eckardt, M.D., Jan M. Feyzi, M.S., Peter Ivanovich, M.D., Reshma Kewalramani, M.D., Andrew S. Levey, M.D., Eldrin F. Lewis, M.D., M.P.H., Janet B. McGill, M.D., John J.V. McMurray, M.D., Patrick Parfrey, M.D., Hans-Henrik Parving, M.D., Giuseppe Remuzzi, M.D.,

The NEW ENGLAND JOURNAL of MEDICINE

Effect of Cinacalcet on Cardiovascular Disease in Patients Undergoing Dialysis

The EVOLVE Trial Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

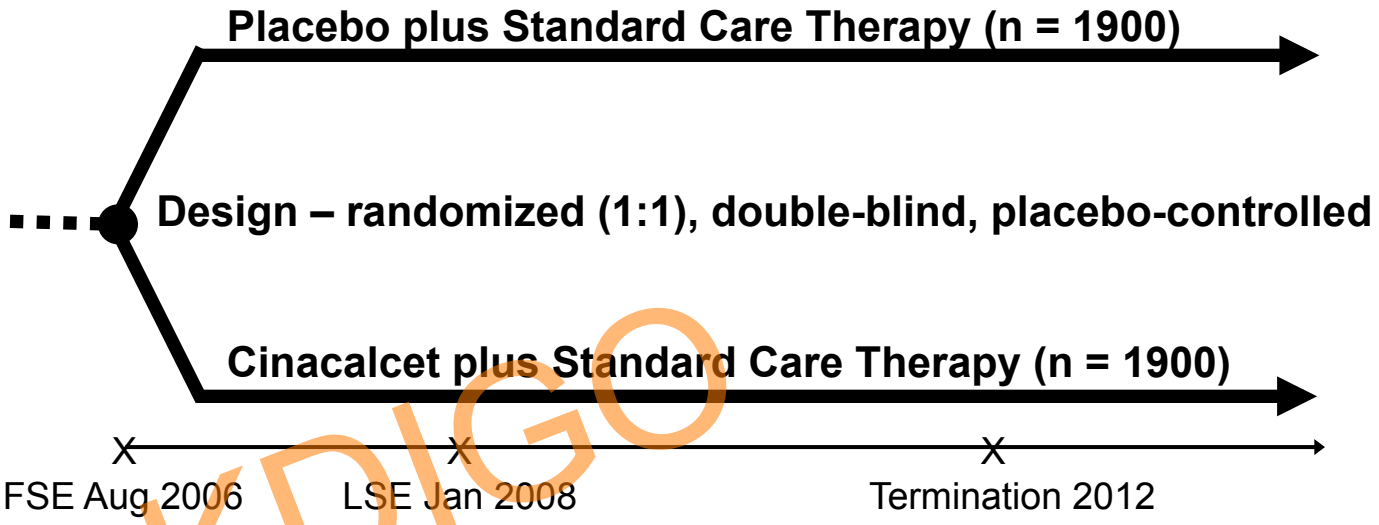
Treatment of Anemia with Darbepoetin Alfa in Systolic Heart Failure

Karl Swedberg, M.D., Ph.D., James B. Young, M.D., Inder S. Anand, M.D., Sunfa Cheng, M.D., Akshay S. Desai, M.D., Rafael Diaz, M.D., Aldo P. Maggioni, M.D., John J.V. McMurray, M.D., Christopher O'Connor, M.D., Marc A. Pfeffer, M.D., Ph.D., Scott D. Solomon, M.D., Yan Sun, M.S., Michal Tendera, M.D., and Dirk J. van Veldhuisen, M.D., Ph.D., for the RED-HF Committees and Investigators*

EVOLVE™

Study Population

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



Primary Endpoint

Time to composite event:
- All-cause mortality
- Myocardial infarction
- Hospitalization for unstable angina
- Heart failure
- Peripheral vascular event

Secondary Endpoints

- Clinical bone fracture
- Parathyroidectomy
- Cardiovascular mortality
- Stroke
- Individual components of primary endpoint

Standard Care Therapy Includes Flexible use of:

- Vitamin D sterols
- Phosphate binders

FSE = first subject enrolled; LSE = last subject enrolled.

Chertow GM, et al. *Clin J Am Soc Nephrol.* 2007;2:898-905.

EVOLVE™ Study Objectives

- Primary: To determine the efficacy of a secondary HPT treatment regimen including cinacalcet compared to a treatment regimen not including cinacalcet (placebo) on the composite of time to all-cause mortality or first non-fatal cardiovascular event (myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular event)

Data on file, Amgen.

EVOLVE™ Study Objectives (continued)

- Secondary: To assess the effects of a secondary HPT treatment regimen including cinacalcet versus a treatment regimen not including cinacalcet, by determining:
  - All-cause mortality
  - Cardiovascular mortality
  - Fatal and non-fatal MI
  - Fatal and non-fatal hospitalization for unstable angina
  - Fatal and non-fatal HF event
  - Fatal and non-fatal peripheral vascular event
  - Fatal and non-fatal stroke
  - Bone fracture
  - Parathyroidectomy
  - The safety and tolerability of cinacalcet

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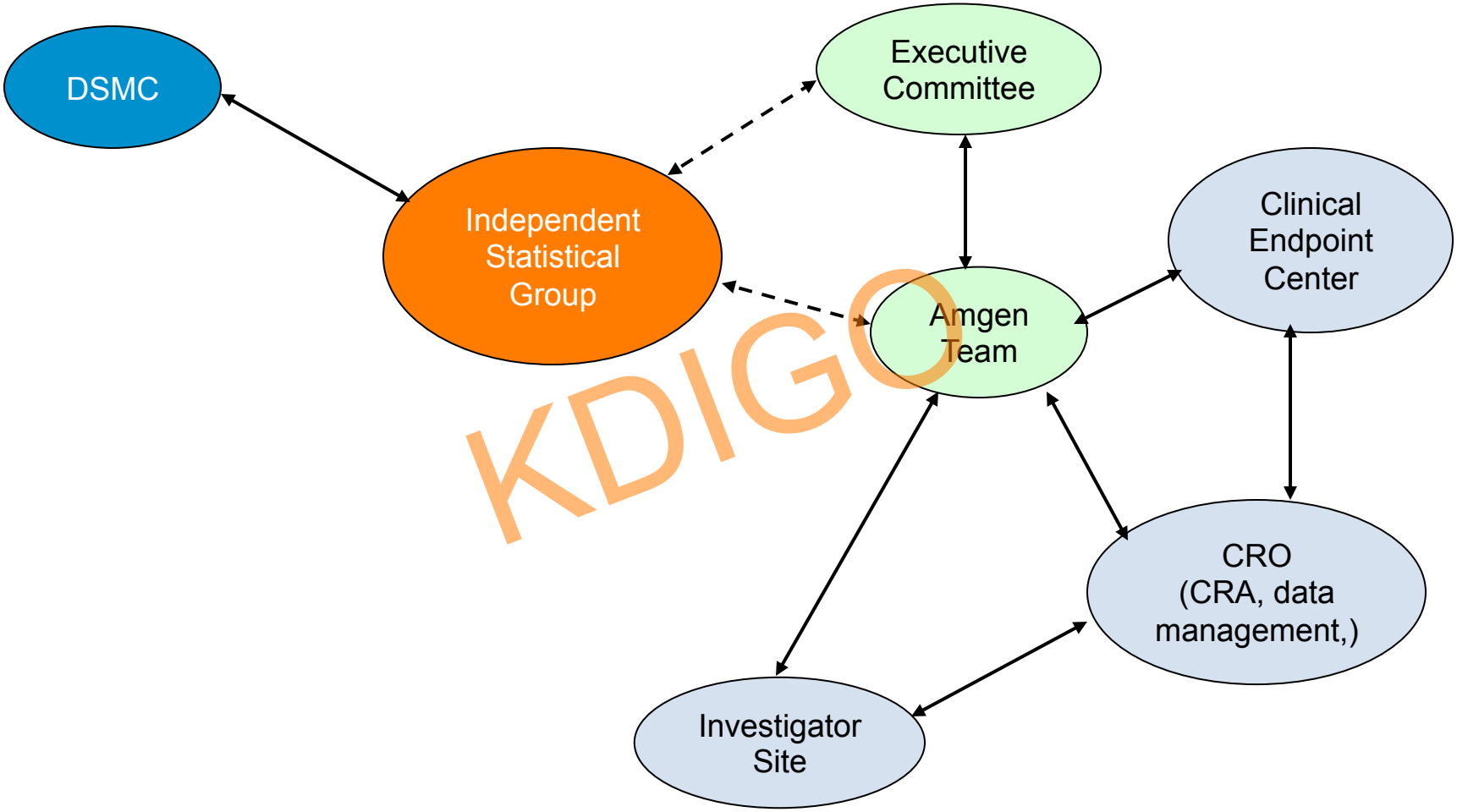
EVOLVE™ Study Objectives (continued)

- Other: The study will also assess the effects of cinacalcet on:
  - The composite event comprising of cardiovascular death, MI, hospitalization for unstable angina, or HF
  - Achievement of NKF-K/DOQI™ Metabolism and Disease recommended targets for intact parathyroid hormone (PTH), serum Ca x P, calcium, and phosphorus levels
  - Percent change from baseline in PTH, Ca x P, serum calcium, and serum phosphorus
  - Health Resource Utilization per subject follow-up time including number and duration of all-cause and cause-specific hospitalizations
  - Assess the patient reported outcomes following a study event using the EQ-5D

Data on file, Amgen.

Committees



DSMC – Data Safety Monitoring Committee

Planned Subgroup Analyses

- Required by regulatory authorities:
  - Age < 65, ≥ 65 years
  - Sex
  - Race (white, black, other)

- Anticipated to have an effect on the treatment benefit:
  - History of diabetes at baseline (yes/no)
  - Region (US, CAN, AUS, EU, RUS, LA)
  - Vitamin D sterol use at baseline (yes/no)
    - ~ 60% received vitamin D sterols at baseline
  - Baseline PTH (300-600,>600-900,>900-1200, >1200 pg/mL)

Data on file, Amgen.

Additional Endpoints/Analyses

- Time to composite event comprising cardiovascular death, MI, hospitalization for unstable angina, or HF event
- % of subjects achieving 2003 US KDOQI™ Goals
  - PTH, Ca, P, and Ca x P
- Change from baseline in PTH, Ca, P, and Ca x P
- Change in EQ-5D™ score from baseline
  - Each time point by treatment arms
  - At time of non-fatal study event
- Health Resource Utilization(HRU)
  - Number and duration of all-cause and cause-specific hospitalizations
- Analyses accounting for events that may occur multiple times
- Analyses of adverse events

Data on file, Amgen.

List of Potential Baseline Covariates (1)

- Age (years) at randomization
- Gender (male, *female)*
- Race (*white*, black, other*)*
- BMI (kg/m^2)
- Blood pressure - systolic/diastolic (mmHg)
- Geographic region (*US, Canada, Latin America, Europe, Russia, Australia)*
- History of (*yes*/no*):*
  - myocardial infarction
  - heart failure
  - coronary artery disease
  - family history of coronary artery disease
  - cardiac arrhythmia
  - hypertension
  - other cardiac disease (as defined by valvular heart disease and angina)
  - stroke
  - transient ischemic attack
  - peripheral vascular disease
  - revascularization
  - endocrine disorder
    - dyslipidemia
    - diabetes
    - parathyroidectomy
  - bone fracture
  - retinopathy

Data on file, Amgen.

List of Potential Baseline Covariates (2)

- Dialysis vintage (years)
- Dialysate calcium (mmol/L)
- Type of vascular access (*natural fistula*, graft, permanent catheter, other)
- Vitamin D use (*yes*/no*)*
- Phosphate binder type (*calcium-containing*, magnesium-containing, aluminum-containing, Sevelamer or lanthanum carbonate)
- Serum calcium corrected for albumin (mg/dL)
- Serum phosphorus (mg/dL)
- Ca x P [$(mg/dL)^2$]
- PTH (pg/mL)
- BALP (µg/L)
- NTx (nmol/L)

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List of Potential Baseline Covariates (3)

- Hemoglobin (g/dL)
- Statin use (*yes*/no*)*
- LDL (mg/dL)
- HDL (mg/dL)
- Total cholesterol (mg/dL)
- Albumin (g/dL)
- Tobacco use (*never*, former, current*)*
- PRO scores (for PRO endpoints only)

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Summary of Results

	Cinacalcet (N=1948)	Placebo (N=1935)	Hazard Ratio	P-value*
Primary endpoint	**938 (48)**	**952 (49)**	**0.93 (0.85, 1.02)**	**0.112**
Death	703 (36)	718 (37)	0.94 (0.85, 1.04)	0.249
CHF	206 (11)	236 (12)	0.82 (0.68, 0.99)	0.034
MI	187 (10)	183 (9)	0.97 (0.79, 1.19)	0.800
HAMI	56 (3)	66 (3)	0.82 (0.58, 1.18)	0.283
Secondary endpoints				
CV death	377 (19)	391 (20)	0.92 (0.80, 1.07)	0.277
Stroke	115 (6)	102 (5)	1.07 (0.82, 1.40)	0.607
Bone fracture	238 (12)	255 (13)	0.89 (0.75, 1.07)	0.218
Parathyroidectomy	140 (7)	278 (14)	0.44 (0.36, 0.54)	<0.001

*Primary endpoint not met; nominal p-values presented for componenets and secondary endpoints

Covariate-adjusted Results

Analysis	HR (95% CI)	Nominal p-value
Unadjusted analysis	0.93 (0.85, 1.02)	0.111
Adjusted for age (years)	0.88 (0.81, 0.97)	0.007
Multivariate best fit model (40 covariates evaluated)	0.87 (0.79, 0.96)	0.006
Multivariate (all 40 covariates included)	0.88 (0.80, 0.98)	0.020

Analysis results for randomized treatment on the primary composite endpoint

"If the only tool you have is a hammer, you tend to see every problem as a nail."

Abraham Maslow (1908-1970)

Outcomes studies in the dialysis population

Study	Arms	Primary Endpoint	n	HR (95% CI)	p-value
4D (NEJM 2005)	Atorvastatin vs Pbo inT2D patients on dialysis	CV mortality, MI, stroke	1255	0.92 (0.77-1.10)	NS
DCOR (KI 2007)	Sevelamer vs CaPB	All-cause mortality	2103	0.93 (0.79-1.10)	NS
AURORA (NEJM 2009)	Rosuvastatin vs Pbo in hemodialysis	CV mortality, MI, stroke	2776	0.96 (0.84-1.11)	NS
IDEAL (NEJM 2010)	Early versus late initiation of dialysis	All-cause mortality	828	1.04 (0.83-1.30)	NS
HEMO (NEJM 2010)	High HD dose vs low High flux vs low	All-cause mortality	1846	0.96 (0.84-1.10) 0.92 (0.81-1.05)	NS NS
SHARP (Lancet 2011)	Simvastatin plus ezetimibe vs Pbo in CKD (D & ND)	First major atherosclerotic event	9270 (D: 3023)	D&ND: 0.83 (0.74-0.94) HD: 0.95 (0.78-1.15)	0.0021 NS
CONTRAST (JASN 2012)	Hemodiafiltration vs hemodialysis	All-cause mortality	714	0.95 (0.75-1.2)	NS
EVOLVE	Cinacalcet vs placebo	All-cause mortality, MI, HUA, HF, PVE	3883	0.93 (0.85, 1.02)	NS

Why aren't more studies designed as LSTs?

- Availability of eligible patients, sites, investigators
- Time
- Cost
- Resources

Simplicity of design and conduct enables size

Incidence/Prevalence, Sample size and Treatment Effect

Disease	Prevalence /Incidence (US)	Name, Sample size	Result	Year
AMI	~1.5 M per year	ISIS-3 n=41,299	35-day mortality: 10.3% aspirin plus heparin vs 10.6% aspirin alone (NS)	1992
CAD	~15 M	4S n= 4,444	RR (death) = 0.70 (0.58-0.85)	1994
Breast Ca	~230,000 per year	Phase 3 study n=469	RR (death) 0.80 (0.64–1.00)	2001
SHPT + dialysis	~100,000	EVOLVE n=3,883	RR (composite endpoint) = 0.93 (0.85 – 1.02)	2012

Why aren't more studies designed as LSTs?

- Need for safety data collection
- Study execution and data collection to meet regulatory requirements
- Interest in more than a single endpoint
- Intellectual curiosity

The concept of LST is well known

- **Large:**
  - Study of interventions with potentially important but moderate benefits
- **Simple:**
  - Minimal inclusion/exclusion criteria
  - Widely practicable intervention(s)
  - Minimal data collection and simple follow-up
  - Unambiguous and readily ascertained endpoints
  - Simple data analyses
- **Trials:**
  - Prospective studies using a randomized design

The seminal paper on LST was published by Yusuf, Collins and Peto in 1984

Advantages and Limitations to Consider

	Key parameters	Small study	Mega trial	LST
1	Complex intervention			
2	Complex endpoint			
	Complex/Precise follow-up			
	Small anticipated treatment effect			
3	Small population			
	Precisely-defined population			
	Expected qualitative interaction			

When could LSTs be used: 3 key conditions for conducting a LST

1. **Although modest, the anticipated effect size will be considered sufficient for securing a new indication**
   - The aim of LSTs is to detect a meaningful but modest effect on one unambiguous and readily ascertained endpoint (eg death, hospitalization)
2. **If the results confirm the primary hypothesis, no additional analyses will be needed**; in particular:
   - Subgroup analyses, to search for qualitative and quantitative interactions will not be performed
   - Post-hoc explanatory analyses will not be performed
3. **The study will only be expected to minimally inform the safety profile of the therapeutic intervention**

These conditions will usually be fulfilled in the context of a post-approval study

TREAT: Trial to Reduce Cardiovascular Events With Darbepoetin alfa Therapy

Hypotheses:

Treatment of anemia with darbepoetin alfa in subjects with chronic kidney disease (CKD) and Type 2 diabetes mellitus decreases mortality and cardiovascular (CV) morbidity

Treatment of anemia with darbepoetin alfa in subjects with CKD and Type 2 diabetes mellitus will delay the progression to ESRD

Study Population

- **Hb ≤ 11 g/dL**
- **eGFR 20-60 mL/min/1.73 m^2**
- **Type 2 DM**

N ~ 2000 **Darbepoetin alfa**

(Target Hb 13 g/dL)

Design –
randomized (1:1), double blind, placebo-controlled

N ~ 2000 **Placebo**

(rescue if Hb < 9 g/dL)

Event-driven: :~1,203 subjects with cardiovascular primary endpoint

Subjects stratified at randomization by
- Baseline level of proteinuria
- History of CV disease
- Study site – for administrative reason, and not used for adjustment in analysis

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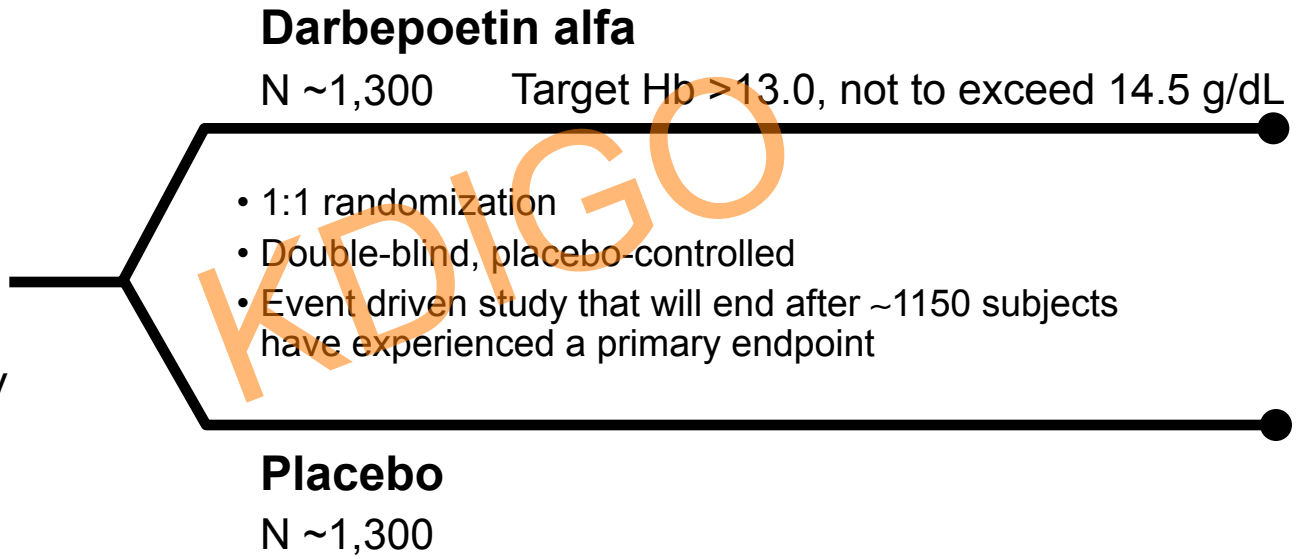
RED-HF Trial Study Design

Hypothesis:

Treatment of anemia with Aranesp® in subjects with symptomatic left ventricular dysfunction decreases the risk of all-cause mortality and hospital admission for worsening heart failure.

Study Population

- Hb 9–12 g/dL (inclusive)
- LVEF ≤ 40%
- NYHA Class II to IV



Primary Endpoint: Time to death from any cause or first hospital admission for worsening HF

Secondary Endpoints

- Time to death from any cause
- Time to CV death or first hospital admission for worsening HF
- Change from baseline to month 6 in KCCQ Overall Summary Score
- Change from baseline to month 6 in KCCQ Symptom Frequency Score

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TREAT Schedule of Assessments (Screening, Year 1-2)

	Screening		Study Period year 1																Study Period year 2													
	Week		Week																Week													
Test	-2	-1	1	3	5	7	9	11	13	17	21	25	29	33	37	41	45	49	53	57	61	65	69	73	77	81	85	89	93	97	101	105
Informed Consent	x																															
Medical History	x																															
Pregnancy Test (Women of child bearing potential)	x																															
Hematology (Reticulocytes, WBC, PLT)	x																															
Anti-erythropoietic protein seroreactivity			x																													
Blood Pressure (5 min resting)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hemoglobin (using point of care device)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hemoglobin (Central Lab Analysis)	x	x	x						x			x			x			x												x		
Investigational Product Dosing			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant Medications	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Iron Therapy	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Events**			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hospitalizaitons			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
RBC Transfusions			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Commercial Erythropoietic Protein Use			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Electrocardiogram			x															x												x		
HbA1c			x									x						x					x						x		
Chemistry (BUN, Creatinine, Albumin, Potassium, CRP)	x		x									x						x					x						x		
Lipids (Cholesterol, Triglycerides, LDL, HDL)			x									x						x					x						x		
eGFR, Spot Urine*	x		x									x						x					x						x		
Ferritin	x		x						x			x			x			x			x		x			x			x		
Tsat	x	x	x						x			x			x			x			x		x			x			x		
HRU, **EQ-5D, FACT-Fatigue (PRO)** questionnaire			x						x			x						x					x						x		
SF-36 (PRO) questionnaire			x									x						x											x		
Six-Minute Walk Test (subset of 1000 subjects)			x									x						x											x		
Physical Exam, waist & hip circumference		x																x											x		
Body Weight	x																	x											x		
Serum, urine samples stored			x															x											x		

KDIGO

*eGFR and spot urine tests will not be performed on subjects who require RRT **Adverse events will be collected from the date of the first dose through one week (7 days) following the date of the last dose of investigational product.

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RED-HF Schedule of Assessments

Test/Procedure		Treatment Phase (expected minimum duration for last enrolled subjects is 6 months)																			
Month						3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Week [b]	Scr	1[c]	3	5	9	11 (13)			25 (27)			37 (39)			51 (53)			63 (65)			75 (77)
Informed consent [d]	X																				
Medical history	X																				
LVEF (if none within 6 months) [e]	X																				
Serum iron, TIBC, Tsat, ferritin	X					X			X			X			X			X			X
Physical exam **(height only at screening)**	X														X						
Vital signs (BP, heart rate) and subject weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hb by modified HemoCue®	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hb by central lab	X					X			X			X			X			X			X
Blood chemistry [f]	X					X			X						X						X
Hematology (RBC, RBC indices, WBC, PLT, reticulocytes, Hb A_{1C}) [g]	X					X			X						X						X
Serum vit. B_{12} & folate	X																				
Concomitant therapy [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum and plasma samples for biomarkers		X							X						X						X
Antibodies to erythropoietic protein		X [i]							X						X						
NYHA functional classification	X					X			X						X						X
Waist circumference	X					X			X			X			X			X			X
Invest. prod. admin.[j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
KCCQ, EQ-5D		X				X			X			X			X						X
Health resource utilization		X							X						X						X
Hospitalizations & endpoints		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] EOS = End of study, ET = Early Termination; [b] Weekly schedule is based on date of first investigational product administration. Alternate weeks for scheduled monthly visits for subjects on schedule are in parentheses; [c] Baseline visit; [d] Written informed consent must be obtained before any screening procedure is performed; [e] If no LVEF within 6 months of randomization, LVEF must be assessed by echocardiogram, radionuclide ventriculography cardiac magnetic resonance imaging, or X-ray contrast ventriculography; [f] Sodium, potassium, blood urea nitrogen, creatinine, glucose, magnesium, calcium, phosphorus, uric acid, total bilirubin, AST, ALT, alkaline phosphatase, albumin, total cholesterol; [g] Hb A_{1C} will only be assessed at screening; [h] Medication use will be assessed at a minimum of every 3 months, procedures will be recorded at every visit, if applicable; [i] Sample must be obtained prior to first administration of investigational product; [j] Investigational product must not be administered until all other visit procedures have been completed; [k] Additional visits will be added with specific assessments at the same frequency if the maximal study duration is longer due to **slower enrollment rate and/or** lower accrual of primary endpoints than expected.

EVOLVE Schedule of Assessments (Screening and Baseline)

Treatments and Procedures	Screening	Day 1 [(d)] (pre-dose)
Informed consent (a)	X	
Vital signs	X	X
Blood pressure and weight		X
ECG	X	
Physical exam	X	
Medical history	X	
Hematology		X
Serum chemistry and lipid profile		X
BALP, NTx		X
25(OH)D and 1,25$(OH)_2$D		X
PTH (b)	X	X
Serum calcium	X	X
Serum phosphorus	X	X
Ca x P	X	X
Serum pregnancy test (females)	X	
PRO (c)		X
Assessment of dialysis dose (spKt/V or URR)	X	
Additional blood samples		X
Blood samples for biomarker development (e)		X
Blood sample for pharmacogenetic analysis (f)		X
Concomitant meds		X
Investigational product dispensation		X

(a) Before any study procedure
(b) Duplicate PTH samples may be collected during the study
(c) PRO assessment can be done within 7 days of day 1
(d) Subjects should be instructed not to eat or drink for at least 8 hours before blood samples are collected.
(e) Selected centers in United States, who received IRB approval for the biomarker development portion of the study, will collect additional blood samples at day 1. These samples will be forwarded to the central laboratory (or designee) to be stored for potential future analyses of additional biomarkers (see Section 7.2.6).
(f) Only if the subject signs a separate informed consent form

EVOLVE Schedule of Assessments (Follow-Up Phase)

Treatments and Procedures	W28	W36	W44	W52 [d]	W60	W68	W76	W84	W92	W100 [d]	W108	W116	W124	W132	W140	W148 [d]	W156	W164	W172	W180	W188	W196 [d]
Informed consent																						
Vital signs				X						X						X						X
Blood pressure and weight				X			X			X			X			X			X			X
ECG				X						X						X						X
Physical exam				X						X						X						X
Medical history																						
Hematology				X						X						X						X
Serum chemistry and lipid profile				X						X						X						X
BALP, NTx				X						X						X						X
25(OH)D and $1,25(OH)_2D$																						
PTH (b)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum calcium	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum phosphorus	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ca x P	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test (females)																						X
PRO (g)				X						X						X						X
Assessment of dialysis dose (spKt/V or URR)				X			X			X			X			X			X			X
Additional blood samples				X						X						X						X
Blood for biomarker development																						
Blood sample for pharmacogenetic analysis																						
Concomitant meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigational product dispensation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

(b) Duplicate PTH samples may be collected during the study

(d) Subjects should be instructed not to eat or drink for at least 8 hours before blood samples are collected

(g) Subjects experiencing a suspected endpoint should complete a PRO assessment at the next scheduled study visit

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Anatomy of a MCT

	EVOLVE	TREAT	RED-HF
Population	Dialysis	CKD-ND, Type II Diabetic	Heart Failure
Subjects Enrolled	3883	4038	2278
Sites Participating	458	623	619
Countries Participating	22	24	32
Study Duration (years)	5.5	5	6.25
CRF pages*	1,320,077	791,000	540,000
Unique CRF pages /subject	148	178	217
Queries	800,741	116,000	50,802
Potential Endpoints Reported	6,657	4200	3000
Type of Investigational Product	Tablet	Injection	Injection
Doses of IP administered	3,748,241	140,535	61,921

* EVOLVE collected data in an electronic data capture system via eCRF
TREAT and RED-HF used paper case report forms for data collection

RCTs could be simplified

- **The main barrier for simplifying mega-trial is the desire to collect a large amount of data, "just in case"**
  - Desire to be able to assess the effects of the intervention in different subgroups
  - Desire to be able to conduct explanatory analyses, if needed
  - Willingness to be able to answer all questions from Regulatory agencies
- **Mega-trials could often be simplified if Regulators agree**
  - Not to ask *a posteriori* for assessment of qualitative and quantitative interactions
  - Not to ask *a posteriori* for explanatory analyses
  - To allow for less extensive collection of AEs after initial approval
  - To be comfortable with limited on-site monitoring

Dialysis Offers an "Ideal" Venue for LST

- Grievous illness with significant unmet need
  - Even treatments with modest effect will be important for this patient population
- Captive Population, seen by HCP TIW
  - Duration of enrollment can be minimized
  - Virtually no lost to follow-up
- High event rate
  - Annual mortality ~20% in the US
  - Allows for relatively short studies
- Almost near complete data-collection in the US
  - Virtually no Lost to F/u
  - Possibility to use EMR for data collection

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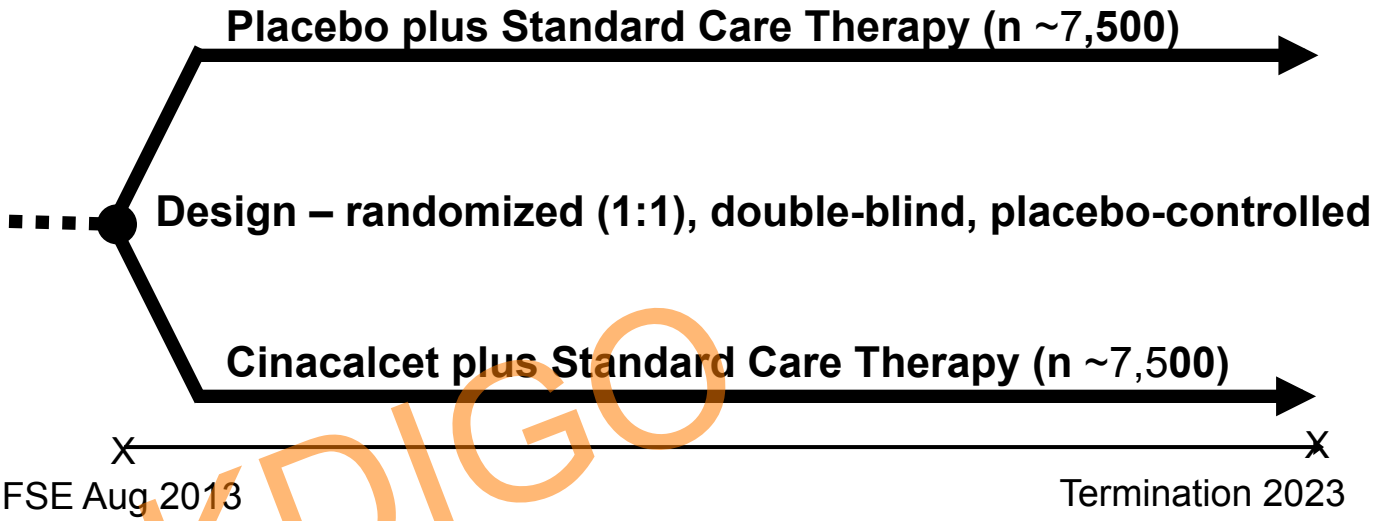
REVOLVE- A Hypothetical LST

REVOLVE
A Hypothetical LST

Study Population

- Adult
- Hemodialysis
- iPTH ≥ 600 pg/mL
- Ca ≥ 8.4 mg/dL



Primary Endpoint

Time to all-cause mortality

Secondary Endpoints

- Clinical bone fracture
- Parathyroidectomy

Standard Care Therapy Includes Flexible use of:

- Vitamin D sterols
- Phosphate binders

FSE = first subject enrolled; LSE = last subject enrolled.

Mock Results

	Cinacalcet (N=1948)	Placebo (N=1935)	Hazard Ratio*	P-value
Primary endpoint				
Death	XX (aa)	YY (bb)	.AA (BB, CC)	.ZZ
CHF***				
MI***				
HAMI				
Secondary endpoints				
CV death				
Stroke				
Bone fracture				
Parathyroidectomy				

EVOLVE FACTS vs REVOLVE Hypothetical Estimates

	EVOLVE	REVOLVE
How many inclusion/ exclusion criteria	17	~4
How many countries	22	~35
How many sites	458	~800
How many CRFs per patient	340	~5
How many CRFs in total	1.320M	~75K
How many DCFs	800,741	~45K
How many endpoints submitted	6,657	~7500
How long from FPE to LPLV	5.5 years	~6-7 years

Summary

- Large trials are enabled by simplicity of design and conduct, without which large trials would not be feasible given time, cost and resource considerations.
- LSTs are appropriate in some, but not all settings. Predicates for LSTs may include
  - Moderate sized, but clinically important treatment effect
  - Prevalent disease
  - In the context of drugs/biologics
    - Post-approval
    - One time intervention or if chronic, easily administered, non-titratable intervention
  - Consequences of reduced monitoring, data collection accepted by all