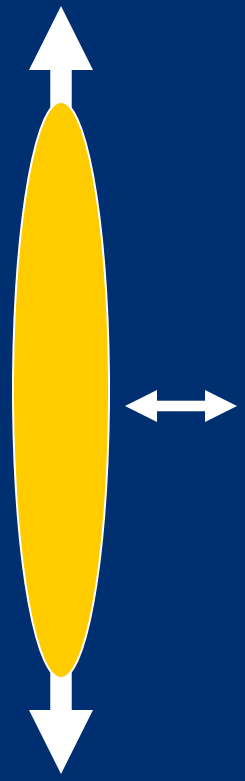
Drug Development: Collaboration between Academia and Industry

José M. Vega, M.D.
Vice President, General Medicine Therapeutic Area
Global Development, Amgen
December 15, 2006

Overview

- Shared Goals of Academic and Industry Investigators
  - Define and Enable Scientific Breakthroughs
- Principles of Academic-Industry Collaboration
- Practical Issues with Academic–Industry Collaboration
- Examples of Successful Academic–Industry Collaborations
- What does the future offer?

Goals of Academic Investigators



- Discover new biology
- Define new understandings of existing biology
- Define potential applications of a discovery
- Translate discoveries into clinical applications

Goals of Industry Investigators

AMGEN

The Intersection of Goals Define and Enable Fruitful Collaboration

Academic Investigators

- Define biology
  - Discovery
- Require access to novel reagents
- Frequently require access to novel assays
- Highly competitive funding process

Industry Investigators

- Enable biology
  - Translation
- Have access to novel reagents
- Often have access to novel assays
- Highly competitive drug development and commercialization process

AMGEN

Principles to Enable Collaboration

- Understand shared goals and expectations of each party
- Define distinct goals and expectations of each party
- Identify potential conflicts of each party
- Define deliverables and anticipated timelines
  - Unequal expectations in this area can cause significant frustration if not clarified
- Establish upfront the use of the data (publications, patents)

Practical Issues with Academic – Industry Collaboration

- Complexity of defining a legal contract
  - Relatively simple for reagents / technology projects
  - More complex for translational projects, particularly clinical projects
- Regulatory requirements
  - Industry investigators must satisfy a multitude of reporting requirements, particularly for clinical projects
- Intellectual property
  - Industry must be fully aware of academic institutional regulations
- Publication guidelines and data access/ownership
  - Develop clear expectations at the start of the collaboration

Examples of Successful Academic – Industry Collaborations at Amgen

- Juvenile Paget's – Osteoprotegerin (OPG) mutation
  - Congenital bone disease
  - Early fractures
  - Deafness
- Lipodystrophy – a form of leptin deficiency
  - Decrease in fat mass (congenital or acquired)
  - Metabolic disturbance (Insulin resistance, diabetes mellitus, hypertriglyceridemia)
  - Neuroendocrine disturbance (hypothalamic hypogonadism)
  - Hepatosteatosis
- Secondary Hyperparathyroidism – common in patients with end-stage renal disease
  - Bone disease, fractures
  - Possible association with increased risk of CV disease

Juvenile Paget's Disease : Osteoprotegerin (OPG) mutation

- Osteoclasts are cells which break down bone
- OPG decreases osteoclast activity
- A deficiency of OPG is linked to an accelerated bone loss leading to fractures
- Hypothesis: Replacing OPG should be capable of reversing this accelerated bone loss

Pilot Study to Determine the Effect of OPG Replacement Therapy

- Collaboration between academic investigators in New Zealand and Amgen
- Opportunity to define this new biology and help these rare patients
- Clear grievous illness and unmet medical need
- Study involved intensive monitoring and evaluation in a small number of subjects – well suited for an academic center
- Might provide support for this pathway in the treatment of other bone disorders (e.g., osteoporosis)

The NEW ENGLAND JOURNAL of MEDICINE

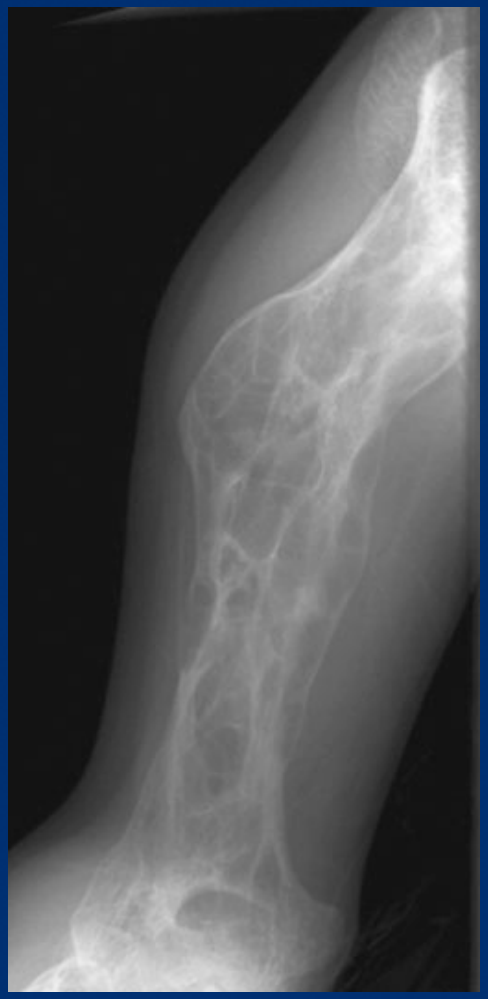
BRIEF REPORT

Recombinant Osteoprotegerin for Juvenile Paget's Disease

Tim Cundy, M.D., James Davidson, Ph.D., Michael D. Rutland, M.B., B.S., Carolyn Stewart, M.M.Sc., and Alex M. DePaoli, M.D.

AMGEN

Osteoprotegerin (OPG) mutation



AMGEN

Response of Patients to OPG Replacement

Table 1. Effects of Long-Term Treatment with Osteoprotegerin on Bone Turnover and Bone Density.*

Variable	Normal Values	Woman, Age 31 Yr		Man, Age 24 Yr	
		Week 0	Week 64	Week 0	Week 64
Osteocalcin (μg/liter)	<45	155	13	178	20
Procollagen I N-terminal peptide (μg/liter)	<60	935	20	1972	20
Bone alkaline phosphatase (μg/liter)	<20	112	15	273	21
Total alkaline phosphatase (U/liter)	30 to 120	352	66	727	79
Parathyroid hormone (pmol/liter)	1 to 6	6.1	7.5	6.2	1.5
N-telopeptide:creatinine	<51	1743	11	2452	11
Bone mineral density (T score)†					
Ultradistal radius	−2 to +2	−4.0	−4.1	−3.6	−3.6
One-third radius site	−2 to +2	−3.8	−3.2	−4.9	−3.4
Skeletal clearance of methylene diphosphonate (ml/min/1.73 m² of body-surface area)	25 to 70	79	50	96	43

AMGEN

Lipodystrophy

- Abnormal amount and or distribution of fat
- Severe metabolic consequences
  - Hypertriglyceridemia
  - Insulin resistance and diabetes mellitus
  - Hepatosteatosis with resultant cirrhosis
  - Abnormalities of pituitary hormones
- Intractable complications unresponsive to traditional therapies
  - Premature death

Pilot Study to Determine the Effect of Leptin Replacement Therapy

- Leptin is a hormone made in fat cells : lacking in lipodystrophy
- Leptin regulates multiple metabolic and neuroendocrine functions
- Animal studies suggested that leptin replacement in models of lipodystrophy reverses the metabolic and neuroendocrine abnormalities
- Productive collaboration developed between Amgen and the NIH and University of Texas-Southwestern

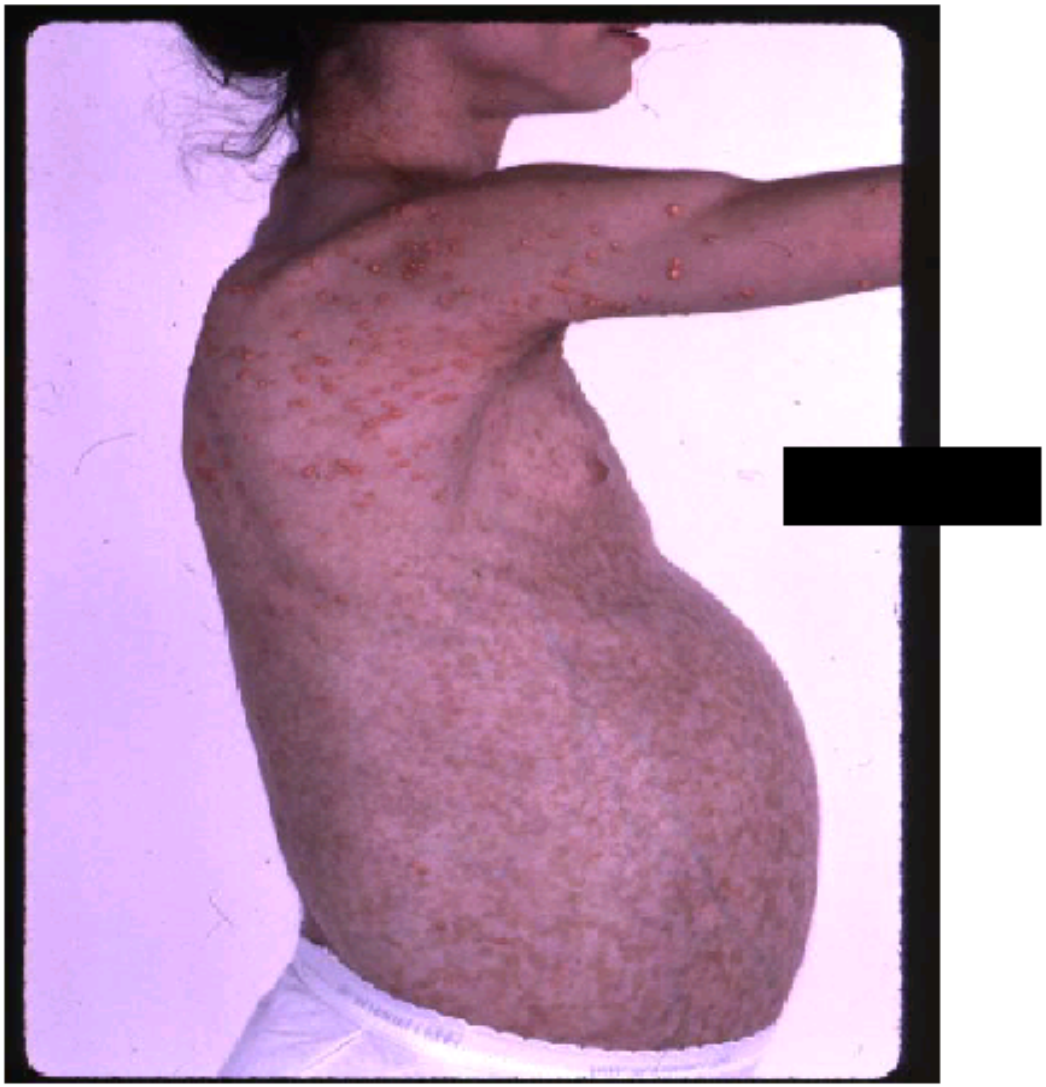
The New England Journal of Medicine

LEPTIN-REPLACEMENT THERAPY FOR LIPODYSTROPHY

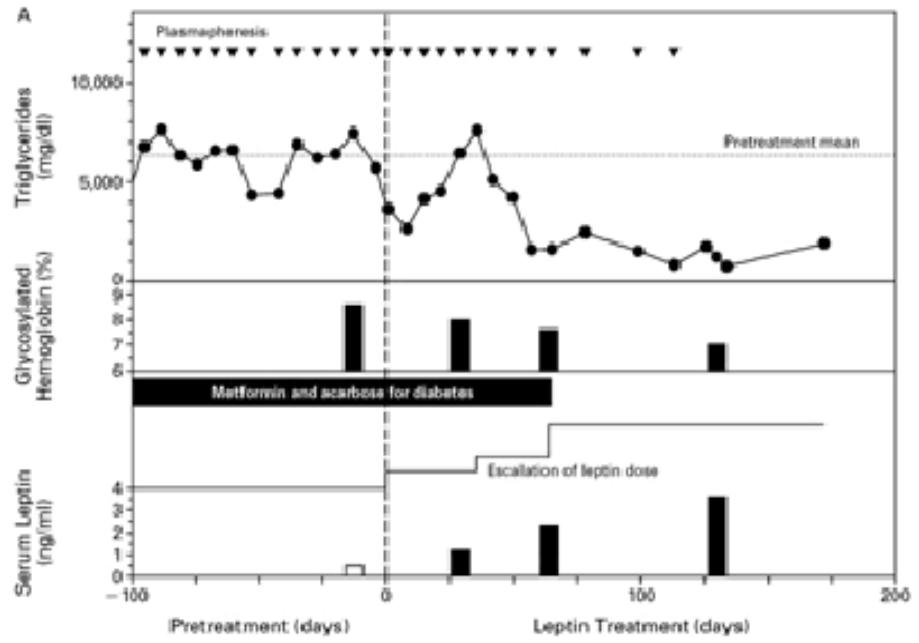
ELIF ARIOGLU ORAL, M.D., VINAYA SIMHA, M.D., ELAINE RUIZ, N.P., ALEXA ANDEWELT, B.S., AHALYA PREMKUMAR, M.D., PETER SNELL, PH.D., ANTHONY J. WAGNER, PH.D., ALEX M. DEPAOLI, M.D., MARC L. REITMAN, M.D., PH.D., SIMEON I. TAYLOR, M.D., PH.D., PHILLIP GORDEN, M.D., AND ABHIMANYU GARG, M.D.

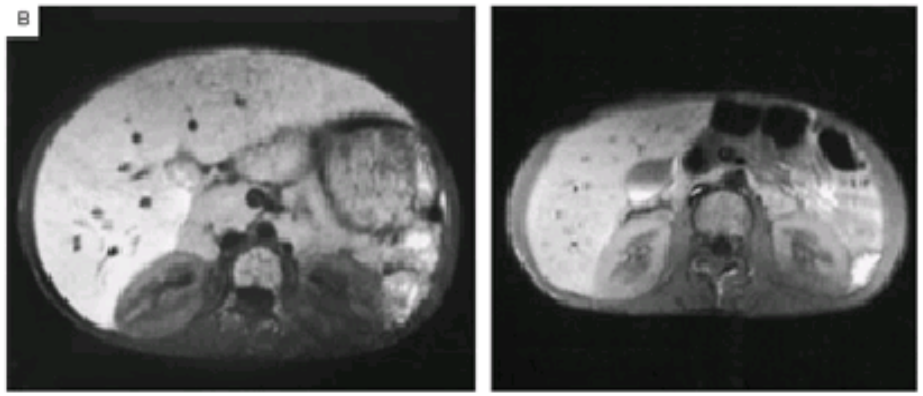
AMGEN

Generalized Lipodystrophy



Effect of R-metHuLeptin in Generalized Lipodystrophy





AMGEN

Significant Benefits to Patients and Greater Understanding of the Biology

- Patients had significantly improved metabolic abnormalities
- Improvement of neuroendocrine abnormalities
  - Hypothalamic amenorrhea
- Quality of life improved
- Collaboration between academic investigators and Amgen advanced the field and increased the scientific understanding of the biology
- Led to further studies in hypothalamic amenorrhea

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Recombinant Human Leptin in Women with Hypothalamic Amenorrhea

Corrine K. Welt, M.D., Jean L. Chan, M.D., John Bullen, B.A., Robyn Murphy, M.S., Patricia Smith, B.S., Alex M. DePaoli, M.D., Aspasia Karalis, B.A., and Christos S. Mantzoros, M.D., D.Sc.

Reproductive Results during r-metHuLeptin Treatment

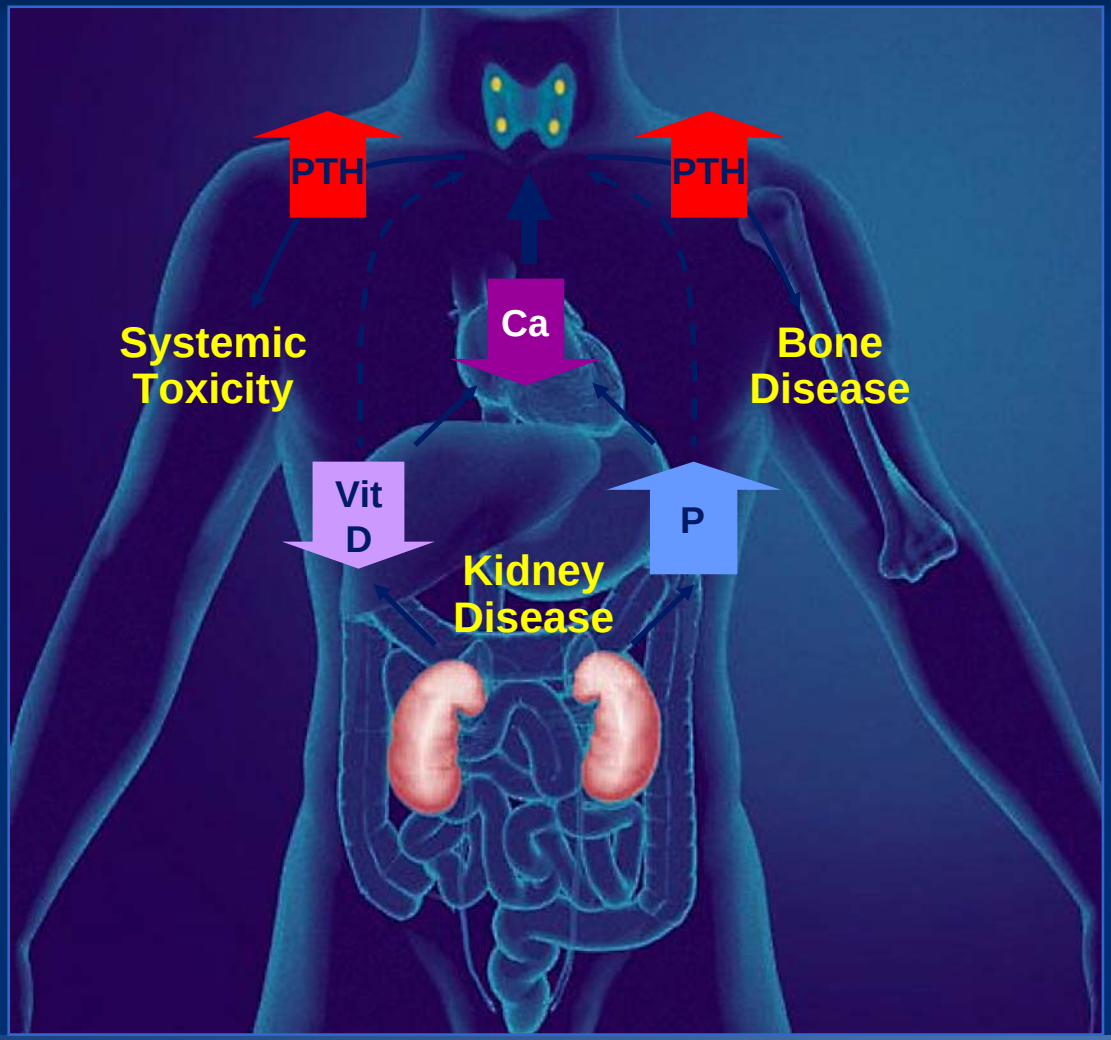
Table 3. Reproductive Data during the One-Month Observation Period and during r-metHuLeptin Treatment.*

Variable	Beginning of Baseline	End of Baseline	Maximum during r-metHuLeptin Treatment
Ovulation (no. of subjects)	0	0	3†
Preovulatory follicle ≥18 mm (no. of subjects)	0	0	5†
Dominant follicle ≥11 mm (no. of subjects)	2	2	6†
Maximal follicular diameter (mm)	9.8±3.3	9.7±2.8	18.0±5.6‡
No. of dominant follicles	0.3±0.5	0.1±0.4	2.4±1.7‡
Ovarian volume (ml)	14.7±6.7	15.5±7.5	22.1±6.7‡
Endometrial thickness (mm)	4.9±2.0	4.3±1.8	7.7±2.0‡

* Plus–minus values are means ±SD.
† $P<0.05$ by the exact binomial test for the comparison with an expected rate of spontaneous ovulation of 10 percent.
‡ $P<0.05$ for the comparison with the end of baseline values.

AMGEN

Secondary Hyperparathyroidism in Chronic Kidney Disease (CKD)

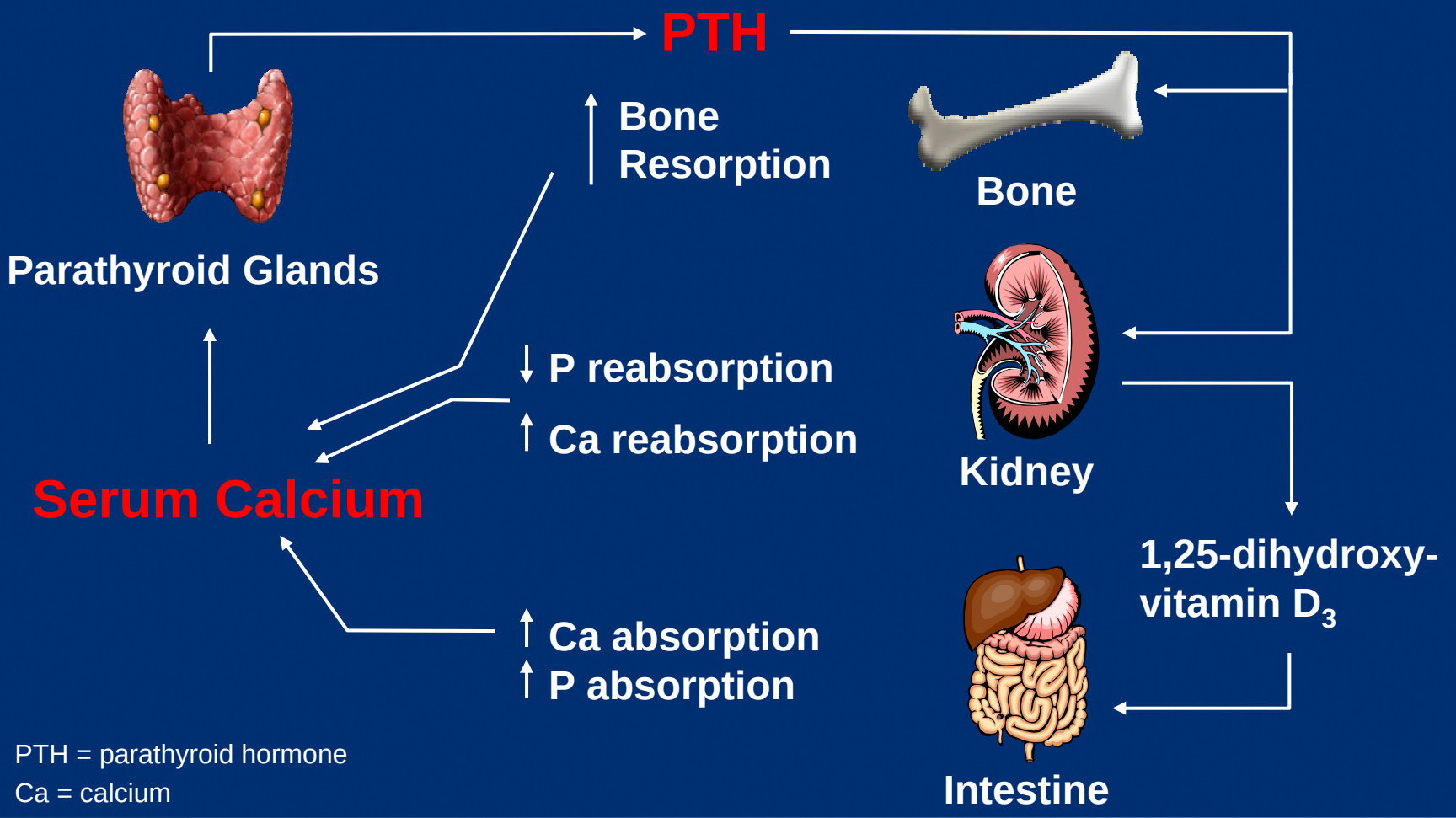


CKD = chronic kidney disease

Skorecki K, et al. *Harrison's Principles of Internal Medicine*. 15th ed. 2001:1551-1562.

AMGEN

Parathyroid Hormone Plays a Central Role in Calcium Homeostasis



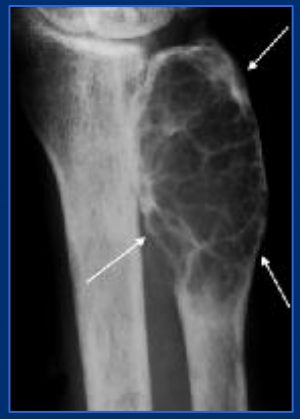
PTH = parathyroid hormone
Ca = calcium
P = phosphorus

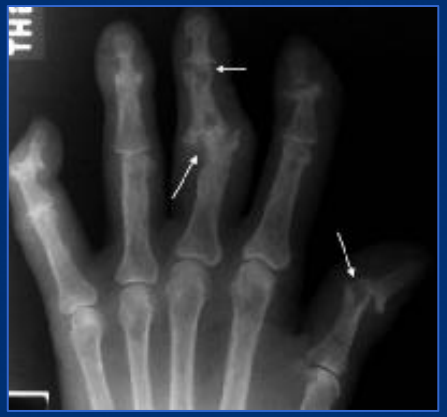
Holick MF, et al. In: Braunwald E, et al, eds. *Harrison's Principles of Internal Medicine*. 15th ed. 2001:2192-2205.

AMGEN

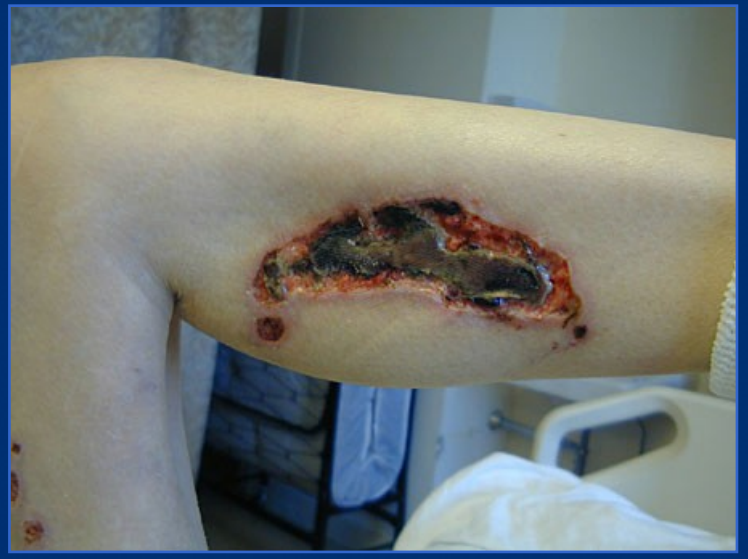
Serious Outcomes Associated With Secondary HPT and Disturbances in Mineral Metabolism

Renal Osteodystrophy

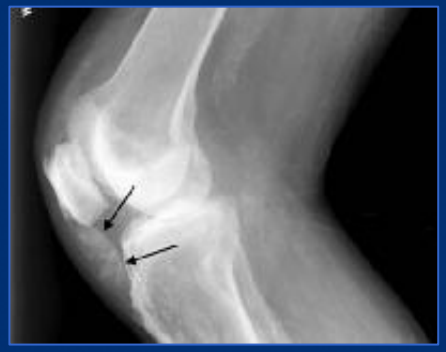


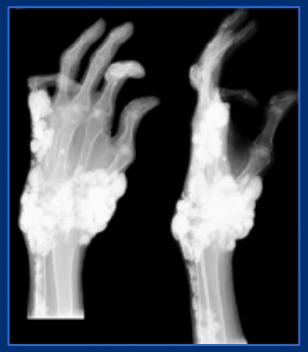


Calciphylaxis



Calcification

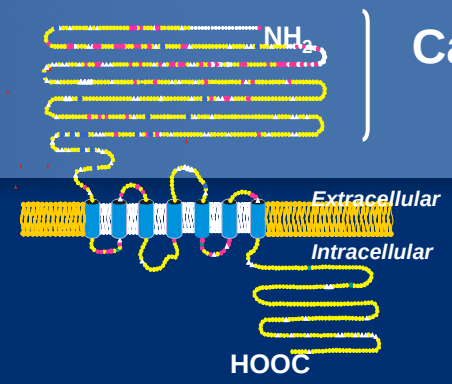




Images from Kline MJ. 2001 Available at http://www.emedicine.com/radio/topic500.htm. Reprinted with permission from eMedicine.com, Inc., 2003.
Image from Richardson ML. 1999. Available at http://www.rad.washington.edu/maintf/cases/unk39/answers.html. Accessed March 1, 2004.
Image from Block GA. 2004.

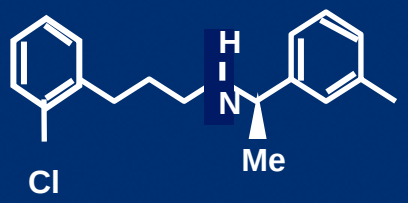
AMGEN

History of Calcimimetics



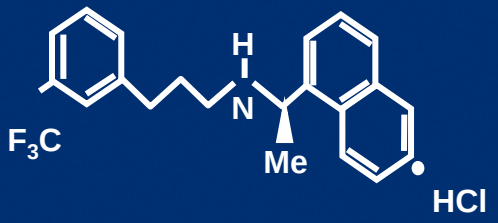
CaR

- 1993: Brown and Hebert cloned the calcium sensing receptor
- Dec. 1993: IND filed by NPS for R-568
- March 1996: Amgen licensed R-568 from NPS
- May 1998: IND filed by Amgen for AMG 073 (cinacalcet HCl)
- Dec. 2001: Phase 3 clinical trials initiated
- Sep 2003: New Drug Application filed with FDA
- Mar 2004: Sensipar® approved and launched in the US



R-568

Cinacalcet



AMGEN

The NEW ENGLAND JOURNAL of MEDICINE

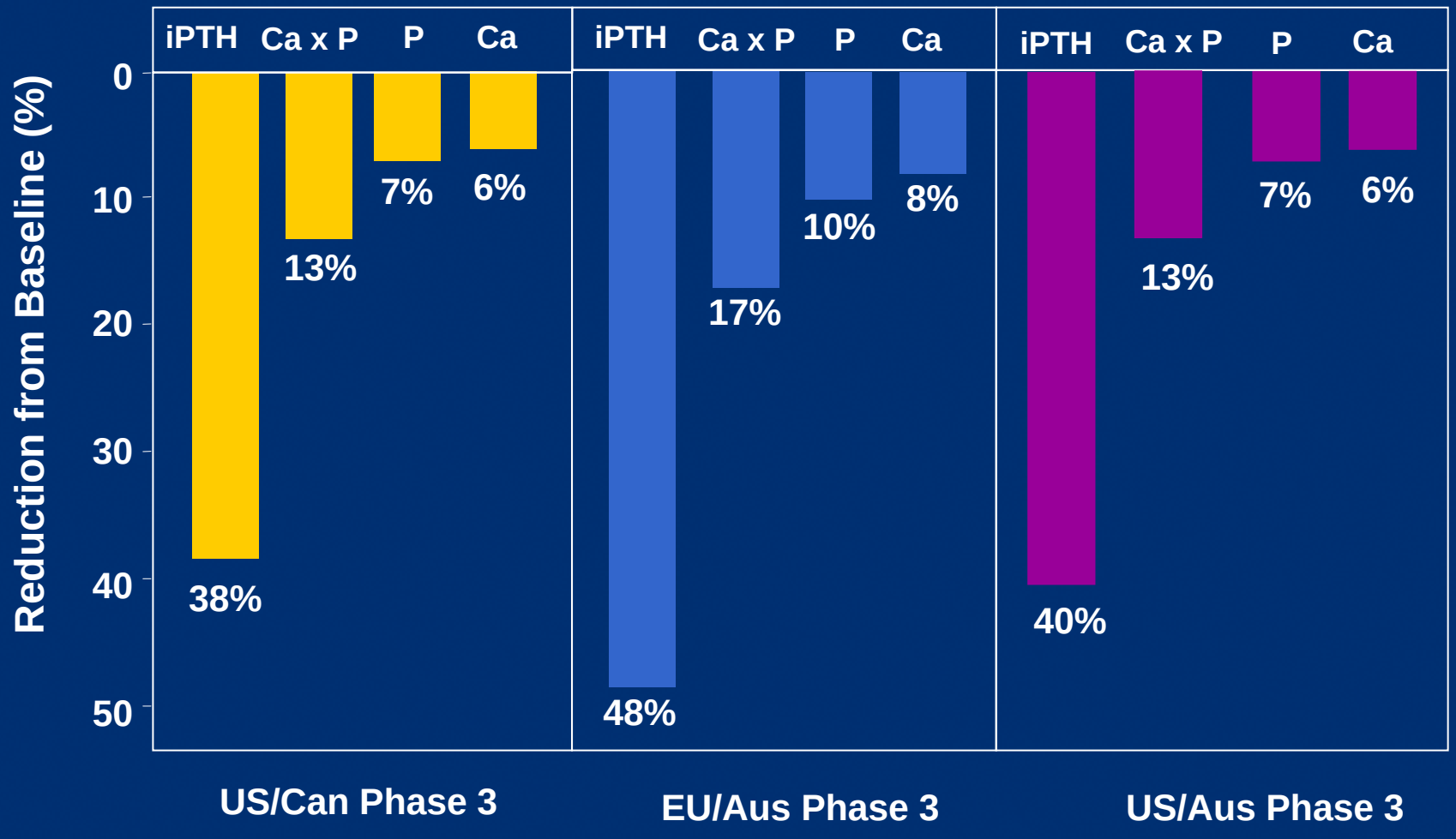
ORIGINAL ARTICLE

Cinacalcet for Secondary Hyperparathyroidism in Patients Receiving Hemodialysis

Geoffrey A. Block, M.D., Kevin J. Martin, M.B., B.Ch., Angel L.M. de Francisco, M.D., Stewart A. Turner, Ph.D., Morrell M. Avram, M.D., Michael G. Suranyi, M.D., Gavril Hercz, M.D., John Cunningham, D.M., Ali K. Abu-Alfa, M.D., Piergiorgio Messa, M.D., Daniel W. Coyne, M.D., Francesco Locatelli, M.D., Raphael M. Cohen, M.D., Pieter Evenepoel, M.D., Sharon M. Moe, M.D., Albert Fournier, M.D., Johann Braun, M.D., Laura C. McCary, Ph.D., Valter J. Zani, Ph.D., Kurt A. Olson, M.S., Tilman B. Drüeke, M.D., and William G. Goodman, M.D.

AMGEN

Cinacalcet Improved All Metabolic Endpoints Across Each Phase 3 Trial



AMGEN

Current Clinical Trial Data Suggest a Benefit of Cinacalcet on Outcomes Including CV Hospitalization 6 & 12 Month Pooled Data

Clinical Outcome	Hazard Ratio* (95% CI)	*P* Value for Hazard Ratio	Cinacalcet HCl (events per 100 subject-years)	Control (events per 100 subject-years)
Parathyroidectomy	0.07 (0.01–0.55)	0.009	0.3	4.1
Fracture	0.46 (0.22–0.95)	0.04	3.2	6.9
Cardiovascular Hospitalization	0.61 (0.43–0.86)	0.005	15.0	19.7
All-Cause Hospitalization	1.03 (0.87–1.22)	0.74	67.0	71.0
Mortality	0.81 (0.45–1.45)	0.47	5.2	7.4
*Control used as reference group				

HR = hazard ratio

Cunningham, et al. Kidney International, 2006

AMGEN

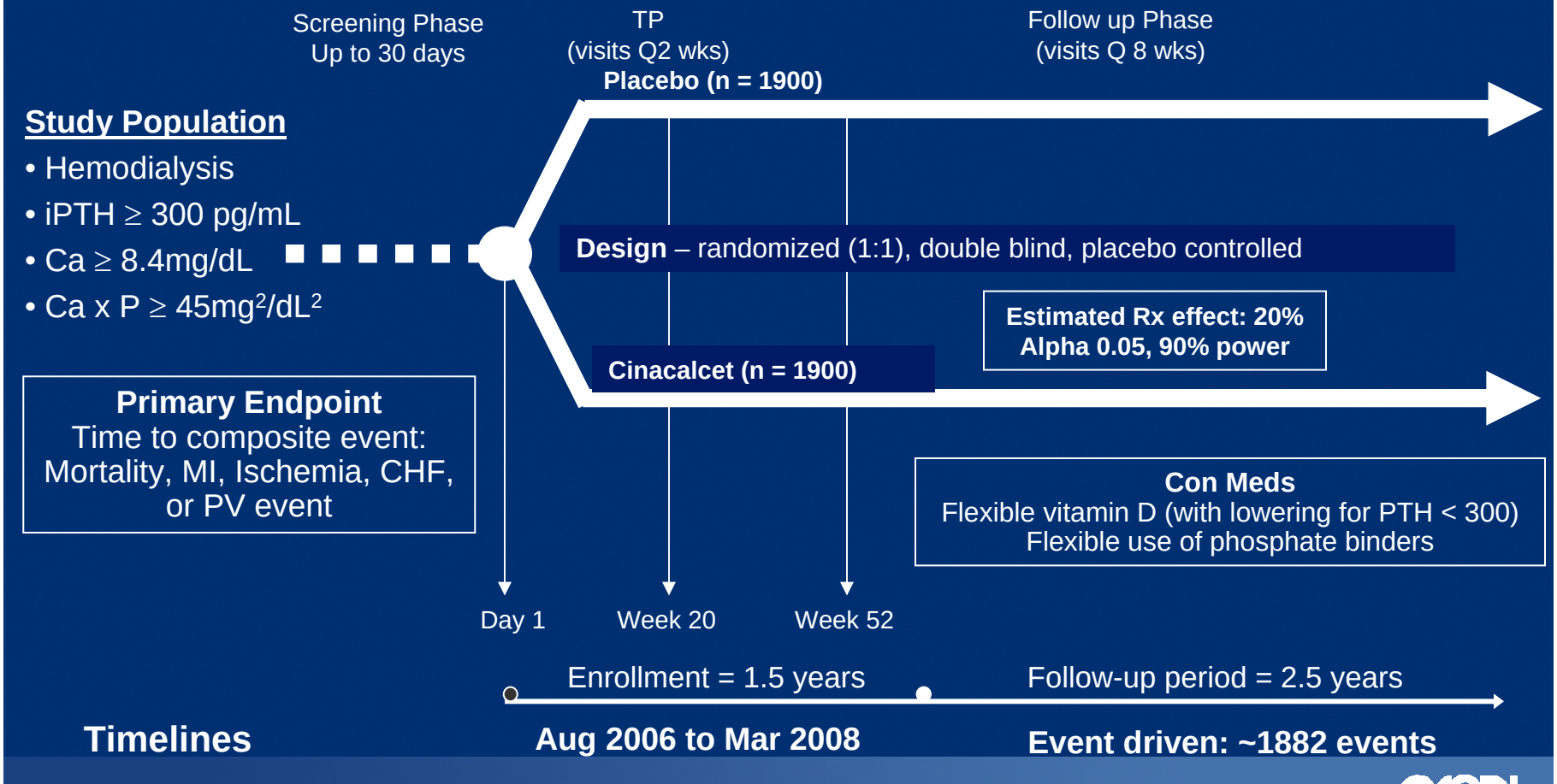
Expert Advise and Support Sought from Academic Nephrology Experts Globally

- Study rationale and draft protocol synopsis with questionnaire to elicit feedback was sent to ~ 150 global nephrology experts
- Team members followed-up with each advisor in teleconferences focused on providing critical input into study design and execution plans
- Meetings with external nephrology experts:
  - ASN Philadelphia, PA: Nov 9, 2005
    - 78 investigators (AUS, US, CAN, EU, and LA)
  - Sao Paulo, Brazil: Dec 3, 2005
    - 40 investigators (ARG, MEX, and BRA)
  - St. Petersburg's, Russia: April 21, 2006
    - 21 investigators (Russia)

AMGEN

Sensipar®/Mimpara® Outcomes Study Design

Hypothesis: A treatment regimen for secondary HPT including cinacalcet reduces the combined incidence of mortality & CV morbidity compared to a treatment regimen without cinacalcet

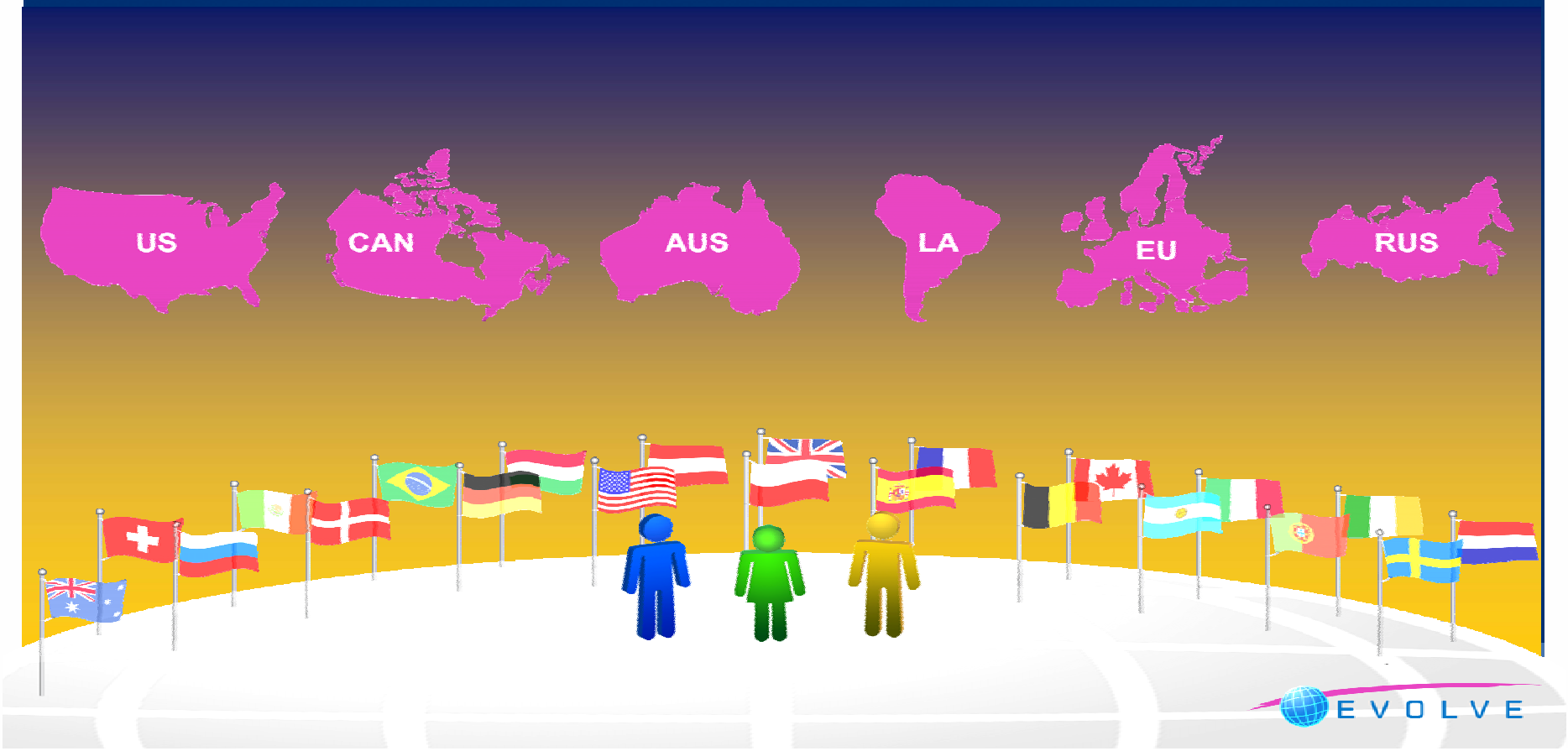


EVOLVE

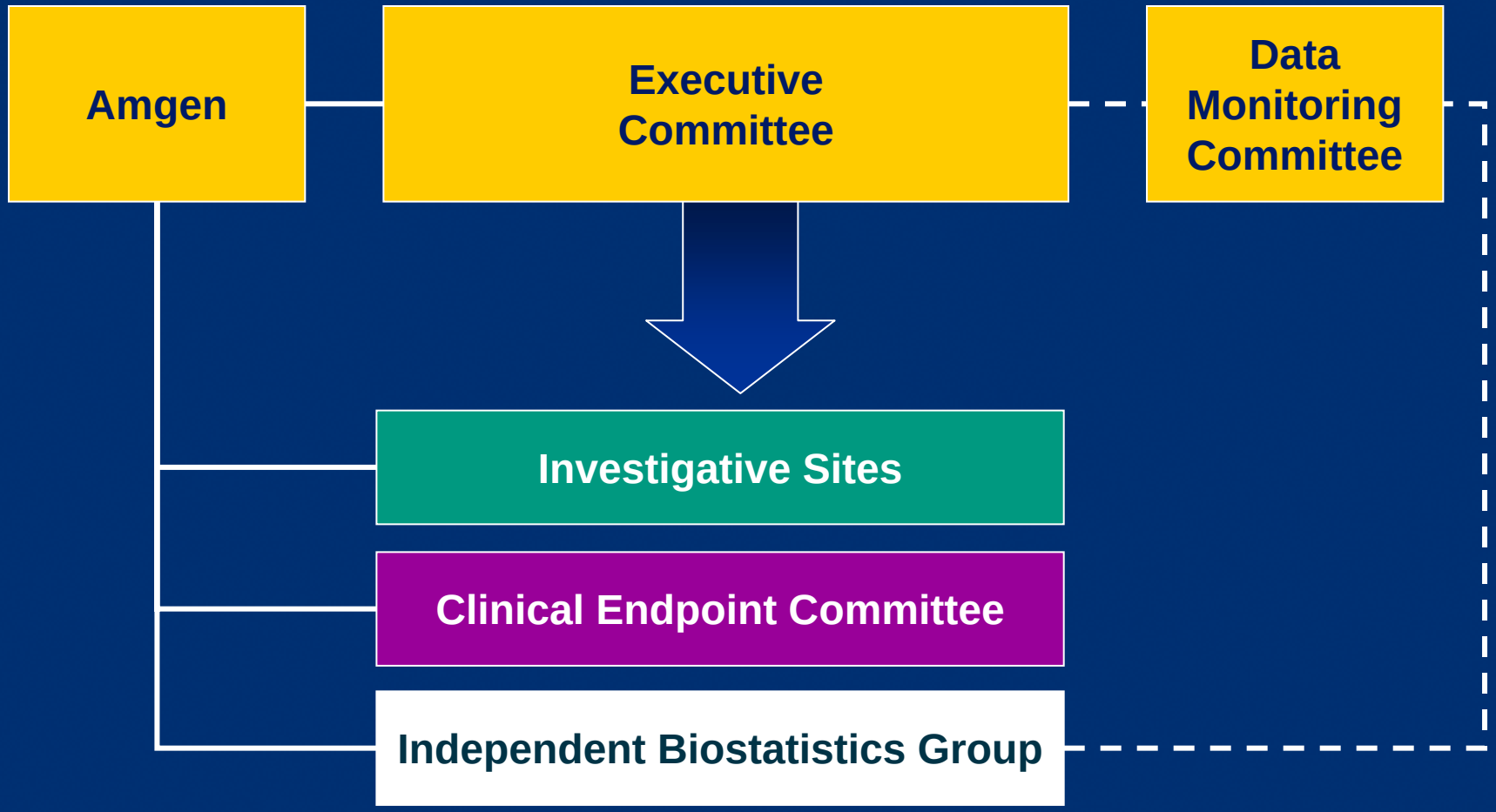
(EValuation Of Cinacalcet HCl Therapy to Lower CardioVascular Events)

A Global Mega-Trial

22 Countries—500 Sites—3,800 Subjects



EVOLVE Governance Overview



EVOLVE Committees & Vendors

Executive Committee	Data Monitoring Committee	Clinical Endpoint Center
Academic/Scientific Oversight of the Study	**Independent Review of Safety Data and Efficacy Interim Analysis**	**Adjudication of all Study Endpoints**
Statistical Data Analysis Center	Investigative Sites	Quintiles
Independent Analysis of Safety and Efficacy Data	**Recruitment of Patients and Ethical Conduct of the Study in Accordance with the Protocol**	**Monitoring and Site Management**
ICON	Central Laboratory *(TBD)*	Central IVRS *(TBD)*
Storage of Additional Lab Samples for Possible Biomarker Development and Genetic Testing	**Analysis and Reporting for Laboratory Samples**	**Subject Randomization and Drug Shipment to Sites**

AMGEN

EVOLVE
An Academic-Industry Collaboration

Glenn Chertow, MD. MPH
Co-Chair
University of CA at SF, USA

Geoffrey Block, MD
Denver Nephrologists, PC, USA

Ricardo Correa-Rotter, MD
Insituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán

Tilman B. Drueke, MD
Necker Hospital, France

Juergen Floege, MD
University Hospital Aachen, Germany

Chris Mix, MD, MS
Amgen, USA

Patrick Parfrey, MD
Co-Chair
Health Sciences Center
St Johns, Canada

Gerard London, MD
Hopital Manhes, France

Ken Mahafey, MD
Duke University, USA

Sharon Moe, MD
Indiana University Hospital, USA

David Wheeler, MD
Royal Free Hospital, United Kingdom

William Goodman, MD
Amgen, USA

AMGEN

EVOLVE Data Monitoring Committee

Charles Hennekens, MD
Chairman
University of Florida
Boca Raton, FL, USA

Colin Baigent, MD
University of Oxford
Oxford, UK

Virgil Brown, MD
Emory University
Atlanta, GA, USA

Peter O'Brien, PhD
Mayo Clinic
Rochester, MN, USA

AMGEN

What Does the Future Offer?

- Increasing legal complexities
- Increasing regulatory complexities
- Increasing scrutiny by the public and the media
- Concerns around potential conflicts of interest
- However, many opportunities exist for productive partnership between academia and the biopharmaceutical industry
  - Hurdles must be overcome jointly to ensure productive ongoing and future academic-industry collaboration.
  - Together, academia and industry can uniquely partner to translate new biology into novel therapeutics to address unmet medical needs and grievous illnesses.