EVENITY™ (romosozumab)

Bone, Reproductive and Urologic Drugs Advisory Committee

Amgen Inc.

January 16, 2019

Introduction

Scott Wasserman, MD

Vice President, Global Development

Amgen Inc.

Overview

- **Despite available therapies, women continue to fracture at an unacceptable rate**
- **Romosozumab provides superior, clinically meaningful anti-fracture efficacy**
- **Cardiovascular risk is uncertain**
  - Imbalance in events observed in one postmenopausal osteoporosis trial, not in other
  - Genetic, non-clinical and additional clinical data do not support risk
- **Benefit/risk is favorable even assuming cardiovascular risk is true**
- **Ensuring a favorable benefit risk in clinical practice: indication, labeling and post-marketing study**

Presentation Overview

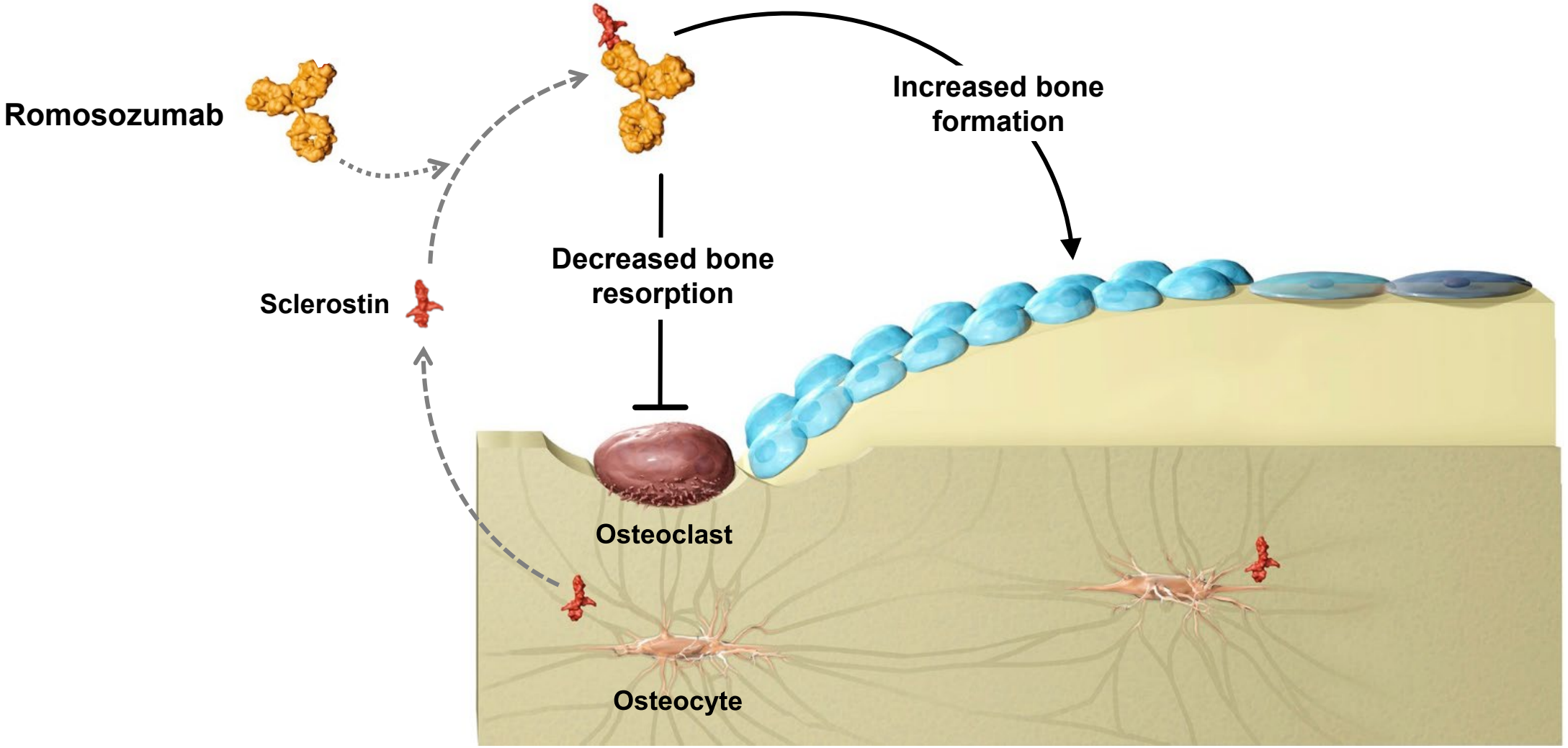
Introduction	**Scott Wasserman, MD** Vice President, Global Development, Amgen
Unmet Medical Need	**Michael McClung, MD** Founding Director, Oregon Osteoporosis Center
Clinical Efficacy	**Rachel Wagman, MD** Executive Medical Director, Global Development, Amgen
Safety and Benefit/Risk	**Scott Wasserman, MD** Vice President, Global Development, Amgen
Amgen Conclusion	**Steven Galson, MD, MPH** Senior Vice President, Global Regulatory Affairs and Safety, Amgen
Clinician Perspective	**Felicia Cosman, MD** Professor of Medicine, Columbia University

Experts

Felicia Cosman, MD	Professor of Medicine at Columbia University College of Physician and Surgeons, Editor-in-Chief of *Osteoporosis International*
Michael McClung, MD	Founding Director, Oregon Osteoporosis Center Adjunct Professor of Endocrinology, Oregon Health & Science University
Matthew Roe, MD, MHS	Faculty Director, Global Outcomes Commercial Megatrials, DCRI Fellowship Program Director Professor of Medicine at Duke University
Marc Sabatine, MD, MPH	Chair of the TIMI Group Lewis Dexter, MD, Distinguished Chair in Cardiovascular Medicine at Brigham and Women's Hospital Professor of Medicine at Harvard Medical School

All are paid consultants to Amgen and have no financial interest in the outcome of the meeting.

Romosozumab Unique Dual Mechanism of Action



Proposed Indication and Treatment

- **Indicated for women with postmenopausal osteoporosis at high risk for fracture, defined as:**
  - History of osteoporotic fracture, or
  - Multiple risk factors for fracture; or
  - Failed or intolerant to other osteoporosis therapy
- **Warnings including Boxed Warning**
  - Romosozumab may increase the risk of myocardial infarction and stroke during treatment
  - Consider benefit/risk in patients with a history of myocardial infarction or stroke
- **Sequential treatment**
  - 210 mg subcutaneous romosozumab once monthly for 12 months followed by antiresorptive therapy

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Osteoporosis: Unmet Medical Need

Michael R. McClung, MD, FACP

Adjunct Professor of Endocrinology

Oregon Health & Science University

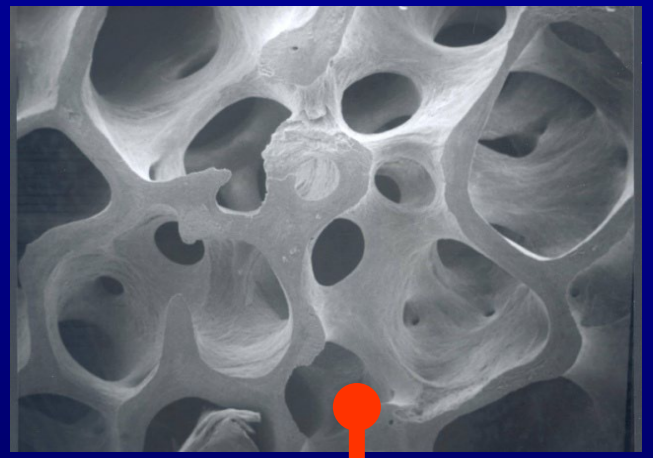
Founding Director, Oregon Osteoporosis Center

Portland, OR

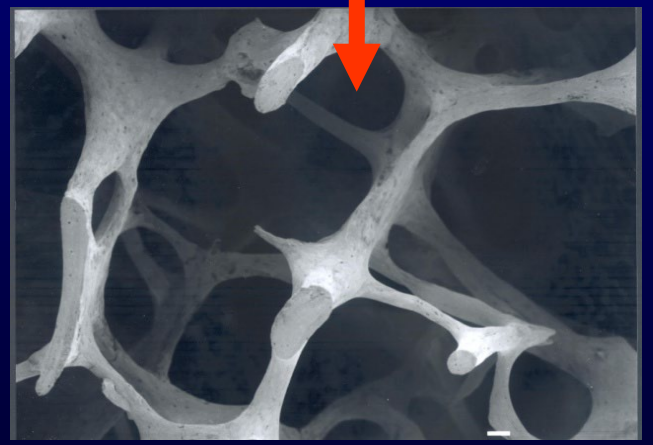
OREGON OSTEOPOROSIS CENTER

Osteoporosis: Progressive Deterioration of Skeletal Structure and Strength[1]

Normal trabecular bone



Osteoporosis

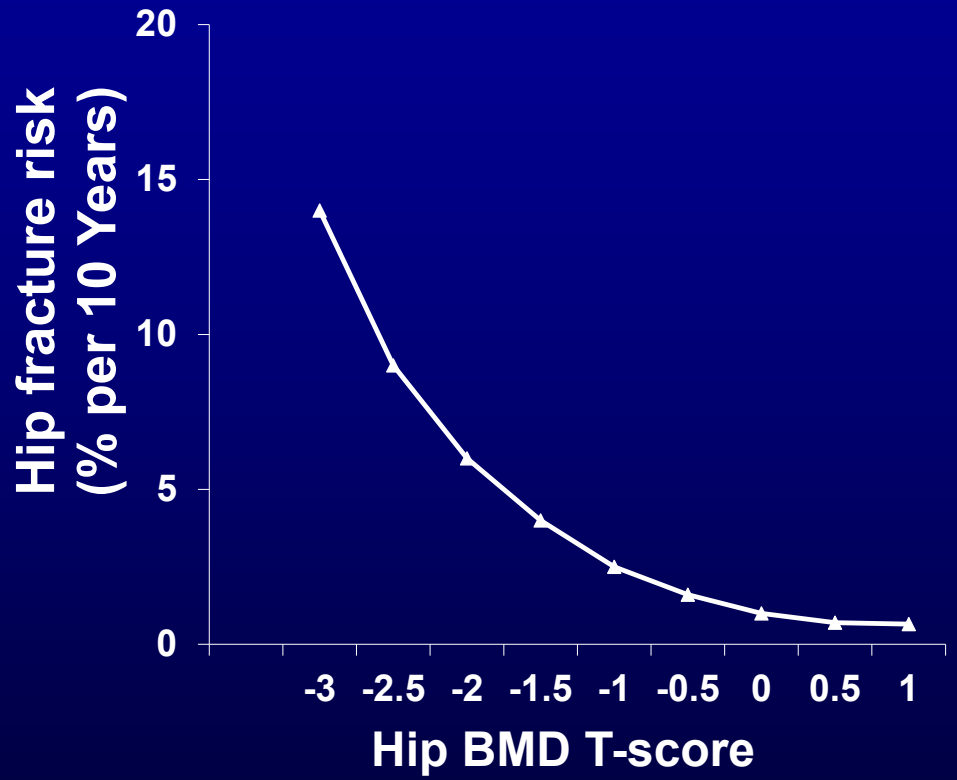


- Loss of bone mass (BMD)
- Deterioration of bone structure
- Impaired strength
- Increased fracture risk

Images Courtesy of Dr. David Dempster

1. Office of the Surgeon General (US) (2004) Bone health and osteoporosis: a report of the Surgeon General. Office of the Surgeon General (US), Rockville (MD). Available from: http://www.ncbi.nlm.nih.gov/books/NBK45513/. Accessed August 2018

Bone Mineral Density Predicts Fracture Risk

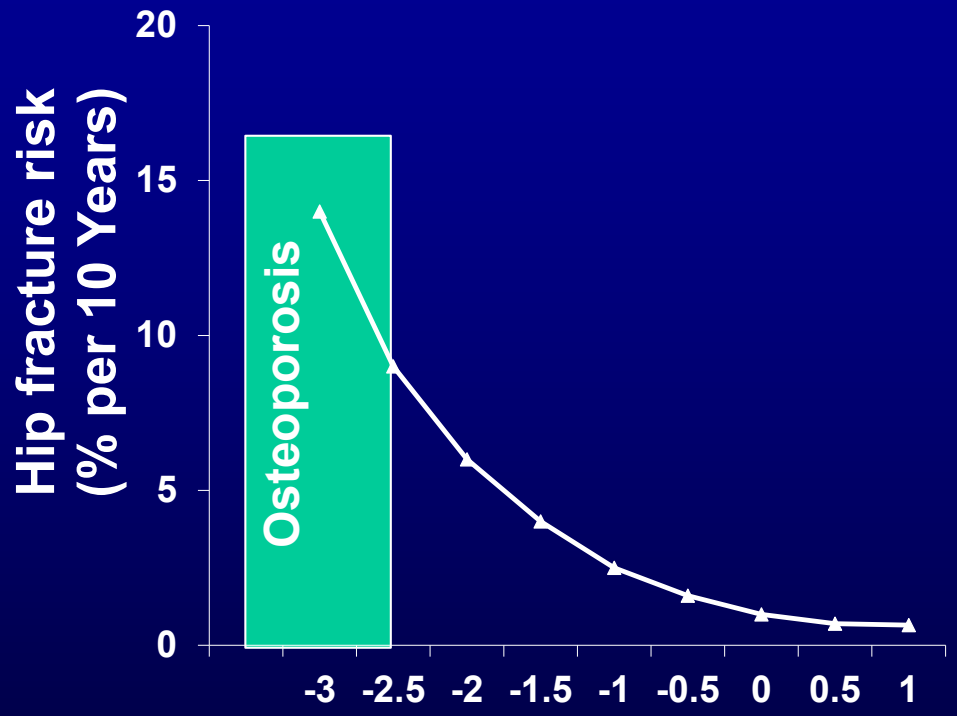


- For every standard deviation decrease in hip BMD, hip fracture risk increases by 2.6-fold in un-treated patients[1]
- Combining risk factors improves fracture risk assessment[1]
- Recent data demonstrates a relationship between on-treatment hip BMD and current fracture rates[2,3]

Core data from Kanis JA, et al. *Osteoporos Int* 2001;12:989–95

1. McClung MR. *Current Osteoporos Reports*. 2005;3:57-63. 2. Cosman F, et al. *JCEM.* 2014:99:4546-4554. 3. Ferrari S, et al. Presented at: ESCEO; April 14-17, 2016; Malaga, Spain.

Diagnosing Osteoporosis



The diagnosis of osteoporosis is made in postmenopausal women with a

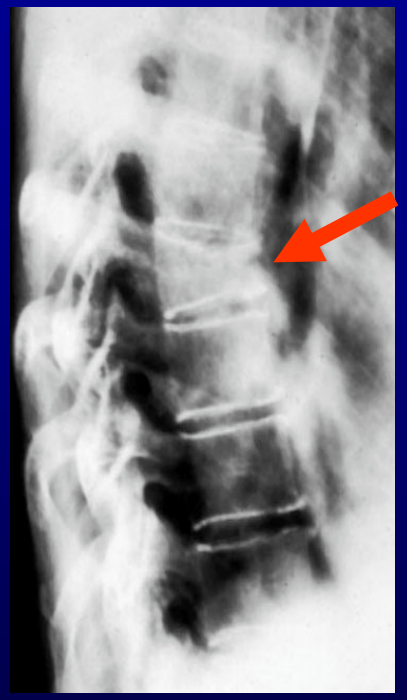
- history of osteoporotic fracture or
- bone mineral density (BMD) T-score value of -2.5 or lower[1]

Core data from Kanis JA, et al. *Osteoporos Int* 2001;12:989–95

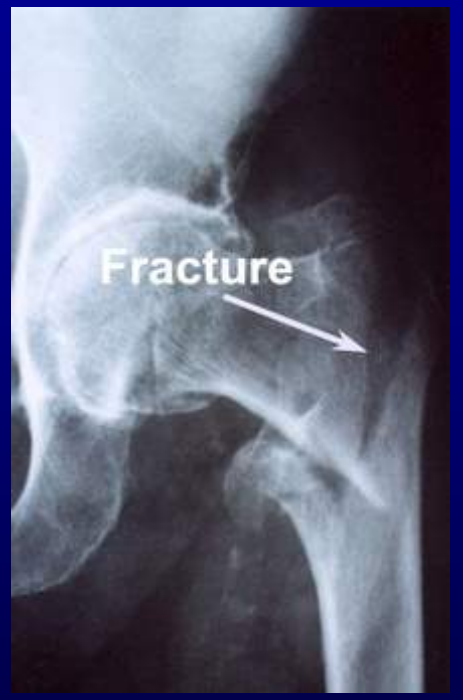
1. McClung MR. *Current Osteoporos Reports* 2005;3:57-63

Clinically Important Fractures Are Common

- Annual incidence of clinically important fractures related to osteoporosis[1,2]
  - 300,000 hip fractures
  - 700,000 clinical vertebral fractures
  - 200,000 proximal humerus fractures
- 432,000 hospital and 180,000 nursing home admissions each year[3]



Vertebral fracture

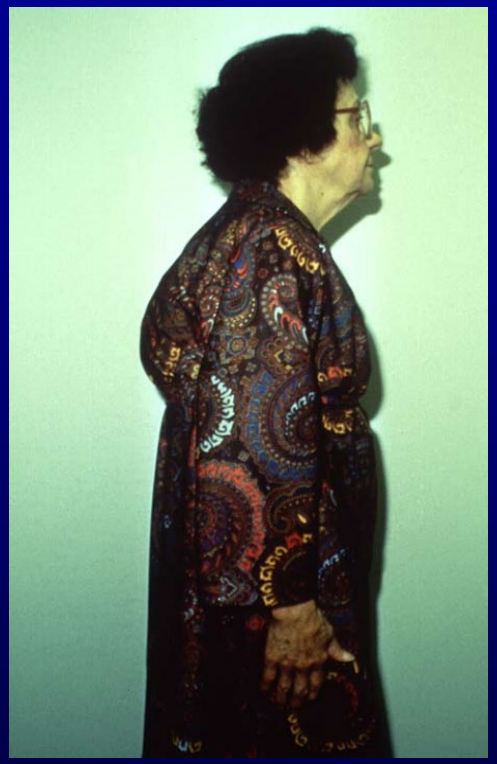


Hip fracture

1. Centers for Disease Control and Prevention. 2016. Available from: https://www.cdc.gov/homeandrecreationalsafety/falls/adulthipfx.html. Accessed August 2018
2. Bartl R, Bartl C. *Bone Disorders.* DOI: 10.1007/978-3-319-29182-6_333. 3. Office of the Surgeon General (US) (2004) Bone health and osteoporosis: a report of the Surgeon General. Office of the Surgeon General (US), Rockville (MD). Available from: http://www.ncbi.nlm.nih.gov/books/NBK45513/. Accessed August 2018

Osteoporotic Fractures Can Be Devastating

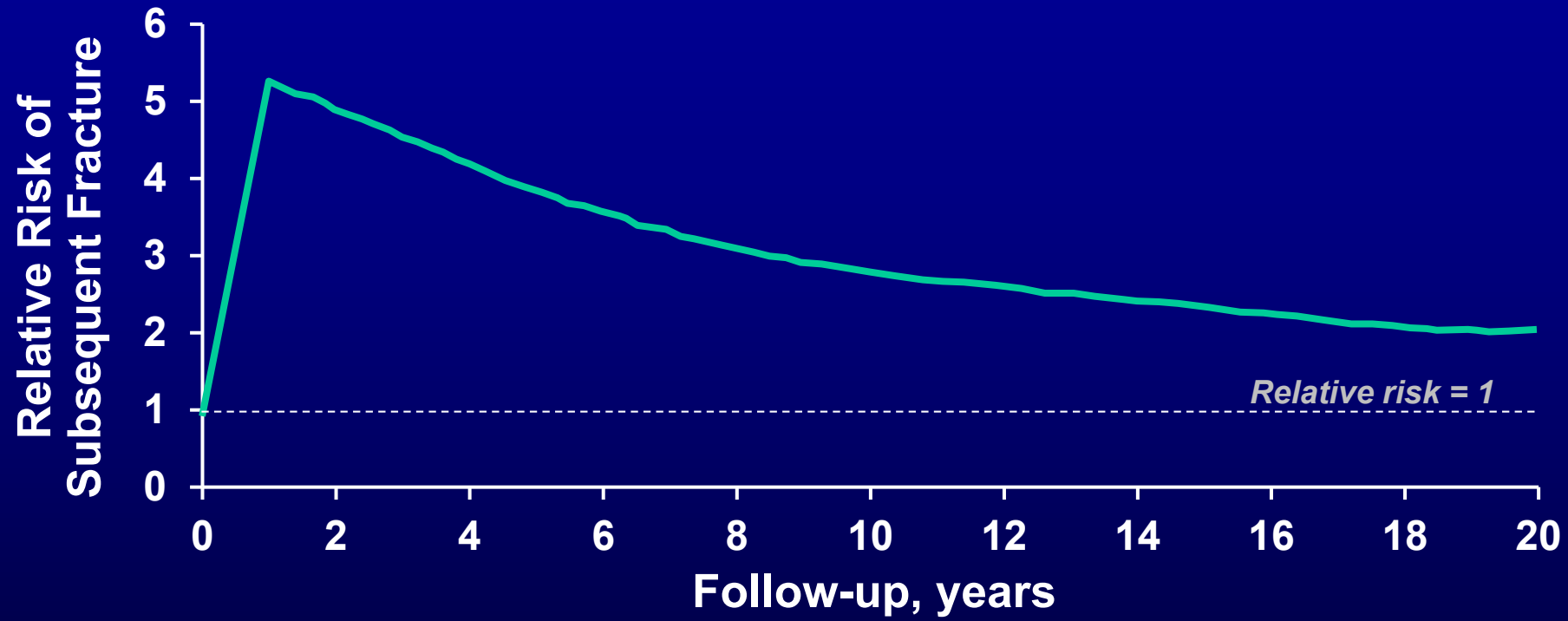
- Increased mortality – 2 to 8-fold increased risk[1,2]
  - 8-36% excess mortality risk within 1 year of a hip fracture[3]
- Substantial morbidity[4]
  - pain
  - impaired mobility
  - reduced pulmonary function
- Loss of independence[5]
- Reduction in quality of life[4,6]
  - change in body image
  - psychosocial distress
  - social isolation



Kyphosis due to vertebral fractures

OOC 1. Cauley JA, et al. *Osteoporos Int*. 2000;11:556-561. 2. Morin S, et al. *Osteoporos Int*. 2011;22:2439-2448. 3. Abrahamsen B, et al. *Osteoporos Int*. 2009;20:1633-1650. 4. Cosman F, et al. *Osteoporos Int*. 2014;25:2359-2381. 5. Bentler SE, et al. *Am J Epidemiol*. 2009;170:1290-1299. 6. Inacio MCS, et al. *Perm J*. 2015;19:29-33

Relative Risk of Recurrent Fracture is Highest in the First Years Following Initial Fracture



There is an urgency in treating patients with recent fractures

Longitudinal study with 4,140 postmenopausal women 50–80 years old with known fracture history
Relative risk was calculated to compare risk of subsequent fracture compared with first fracture
van Geel TACM, et al. *Ann Rheum Dis* 2009;68:99-102

Identifying Postmenopausal Women at High Risk for Fracture[1]

- Prior, especially recent, fracture
- Advanced age
- Multiple comorbidities
- Very low BMD, with or without other risk factors

1. Cosman F, et al. Osteoporos Int. 2014;25:2359-2381

Current Therapies for Postmenopausal Osteoporosis[1]

Class of Agent	MOA	Examples of Agents	Limitations
Anti-resorptive Drugs	Increase BMD and strength by inhibiting resorption	bisphosphonates • alendronate • ibandronate • risedronate • zoledronic acid denosumab raloxifene	• Do not correct structural damage • Takes time to reduce risk of nonvertebral fractures
Bone Forming Drugs (anabolic agents)*	Increase BMD and strength by stimulating bone formation	teriparatide abaloparatide[2]	• Lifetime use limited to 2 years[2]

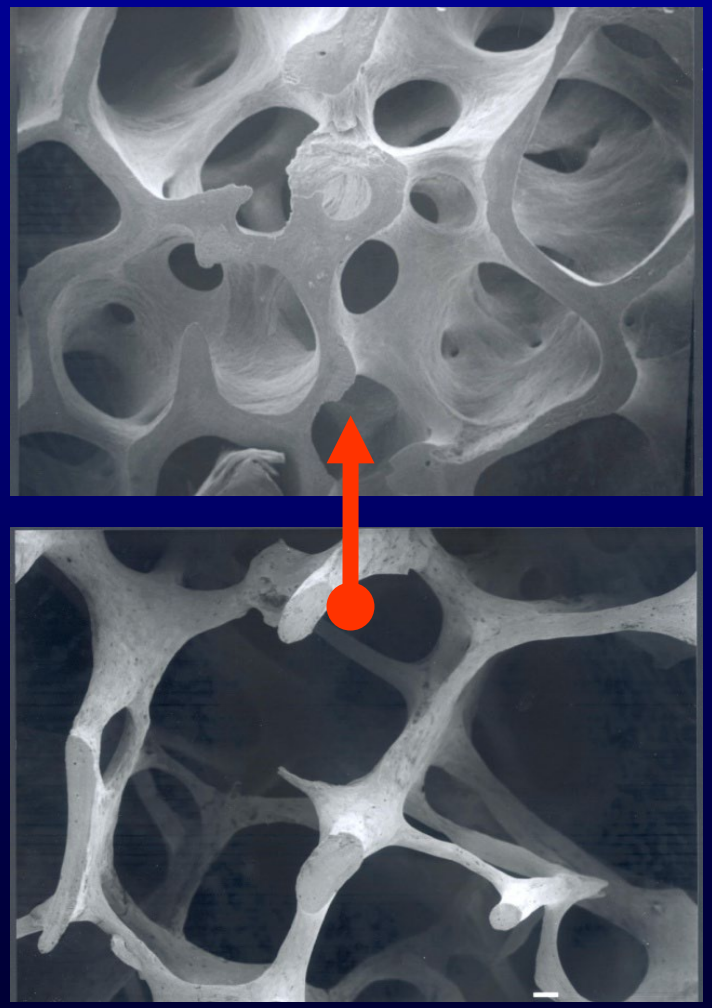
**** Short term bone forming therapy is usually followed by anti-resorptive therapy***

1. Camacho PM et al. *Endocr Pract.* 2016;22(Suppl 4):1-42. 2. Tymlos® (abaloparatide) prescribing information, Radius Health.

Goals of An Improved Osteoporosis Therapy

- To rapidly
  - normalize bone mass and restore architecture
  - increase bone strength
  - reduce fracture risk

- Having romosozumab as a treatment option can help address this need



Images Courtesy of Dr. David Dempster

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Clinical Efficacy

Rachel Wagman, MD

Executive Director, Global Development
Amgen Inc.

Overview

- **Clinical development program**
- **Phase 3 dose selection**
- **Efficacy**
  - Fracture outcome trials
    - » Study 337 vs placebo
    - » Study 142 vs alendronate
  - Bone strength trial
    - » Study 289 vs teriparatide

Clinical Program Overview

19 Studies

Phase 1 (12 Studies)

Healthy subjects comparative bioavailability and bioequivalence (5 studies)

Healthy subjects PK & tolerability (2 studies)

Subject PKD, PK, and tolerability (5 studies)

Phase 2 and 3 (7 Studies)

326 – PM women with low BMD, active comparator, placebo

291 – PMO Japanese women, placebo

337 – Fracture outcomes, placebo, PMO women

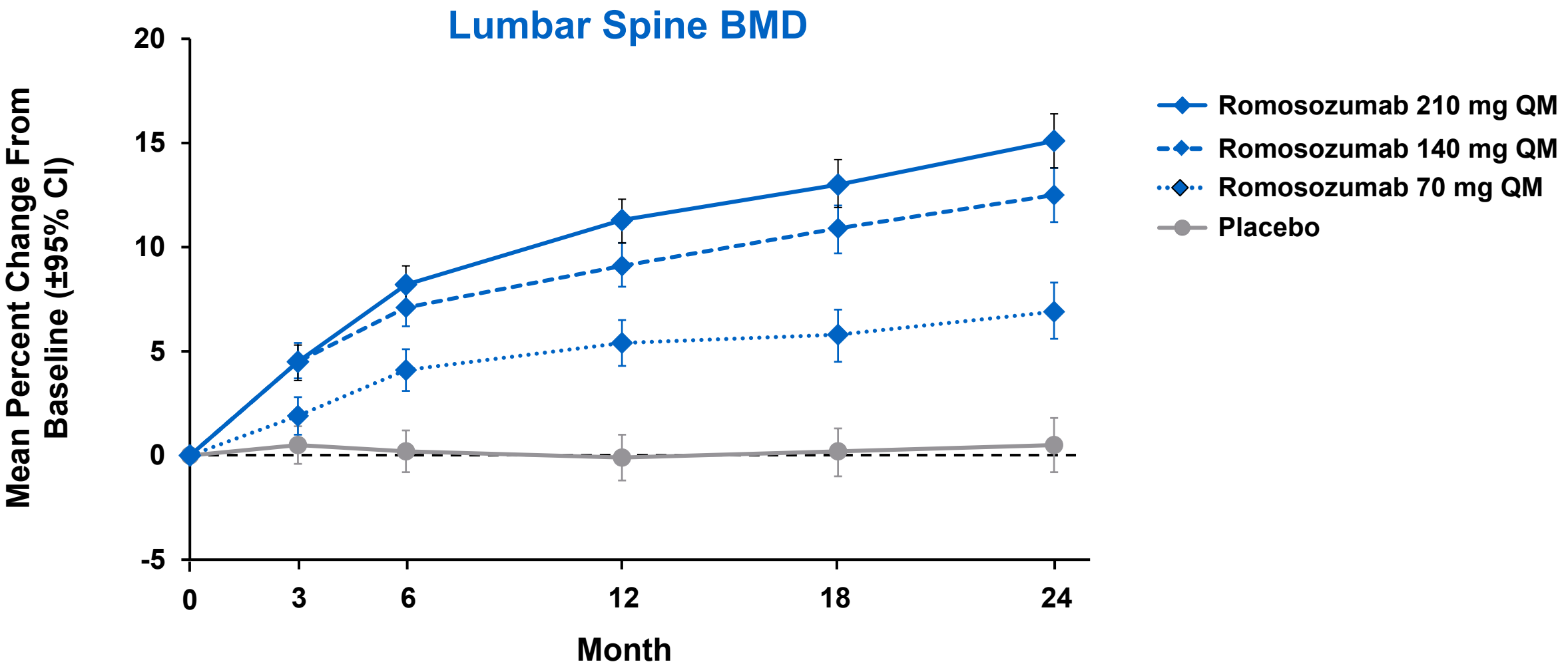
142 – Fracture outcomes, active comparator, PMO women

289 – BMD, active comparator, PMO women pretreated with BP

174 – BMD, placebo**,** men with osteoporosis

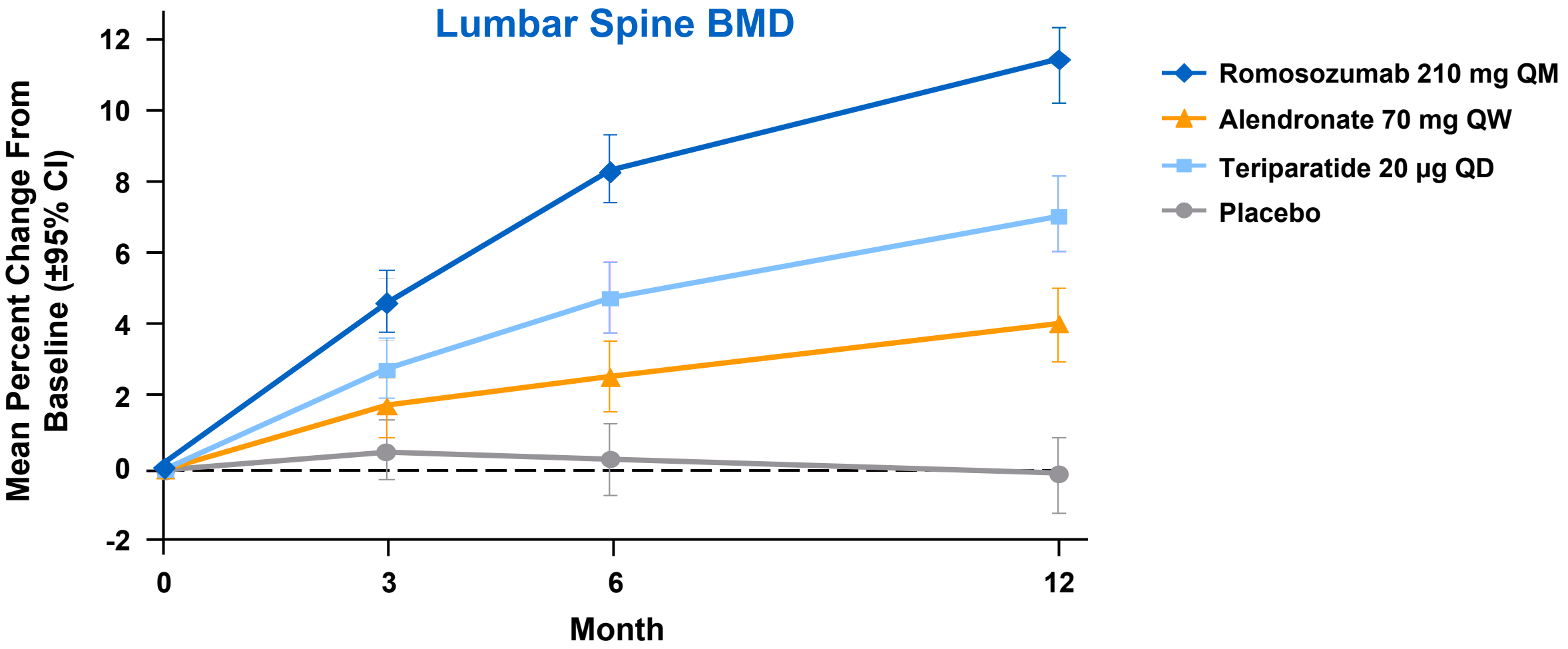
156 – BMD, PMO women

Study 326: Supports Dose of 210 mg QM for 12 Months



P<0.001 for romosozumab 210 mg QM vs placebo at all timepoints.

Study 326: Greater BMD Gains with Romosozumab 210 mg QM versus Alendronate and Teriparatide



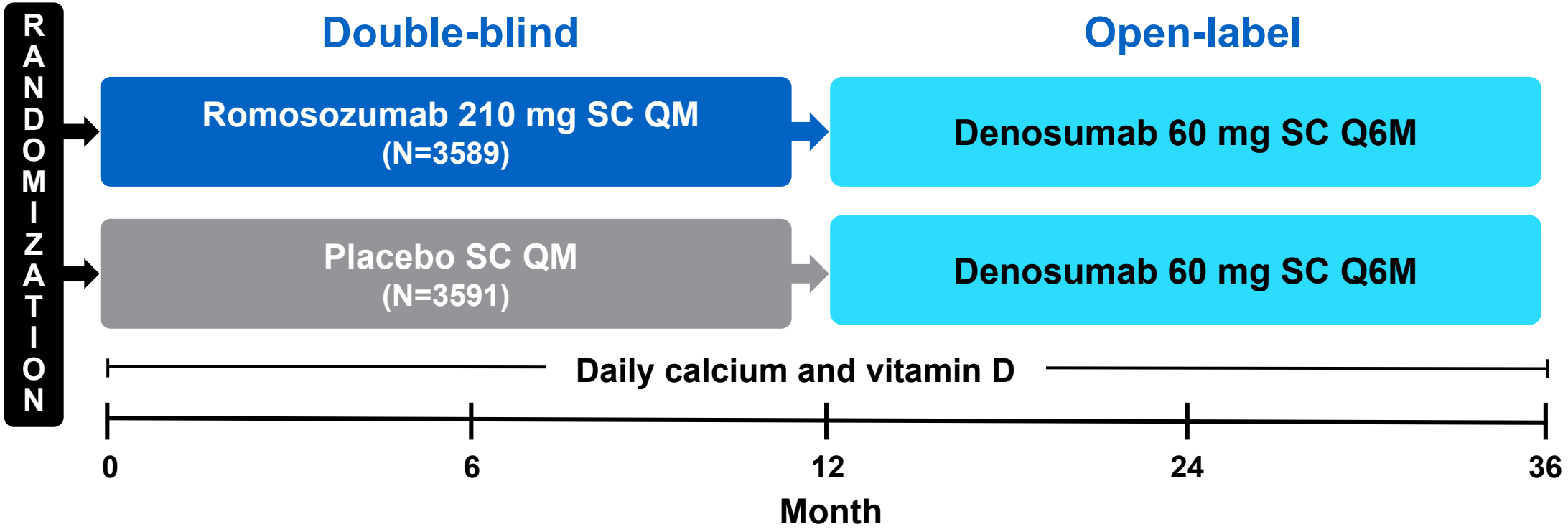
P<0.05 vs all comparators and all timepoints.

Phase 3 Clinical Studies in Postmenopausal Women with Osteoporosis

Study Number	Number of Subjects	Treatment Sequence		Study Duration	Primary Endpoint
		Comparator	Follow-on Therapy		
337	7180	Placebo	Denosumab	36 months	▪ New vertebral fracture at 12 and 24 months
142	4093	Alendronate	Alendronate	Clinical fracture event driven; median 36 months (Q1, Q3; 30, 43)	▪ New vertebral fracture at 24 months ▪ Clinical fracture at the Primary Analysis[a]
289	436	Teriparatide	–	12 months	▪ Percent change total hip BMD through 12 months

[a]Primary analysis was event-driven and occurred at a median follow-up of 33 (Q1, Q3: 27, 40) months.

Study 337: Study Design



Key Entry Criteria:

- T-score > -3.5 and < -2.5 at the total hip or femoral neck
- No history of severe or > 2 moderate vertebral fractures, no hip fracture

Co-Primary Endpoints:

- New vertebral fracture at 12 and 24 months

Key Secondary Endpoints:

- Clinical, non-vertebral, and other fracture categories at 12 and 24 months

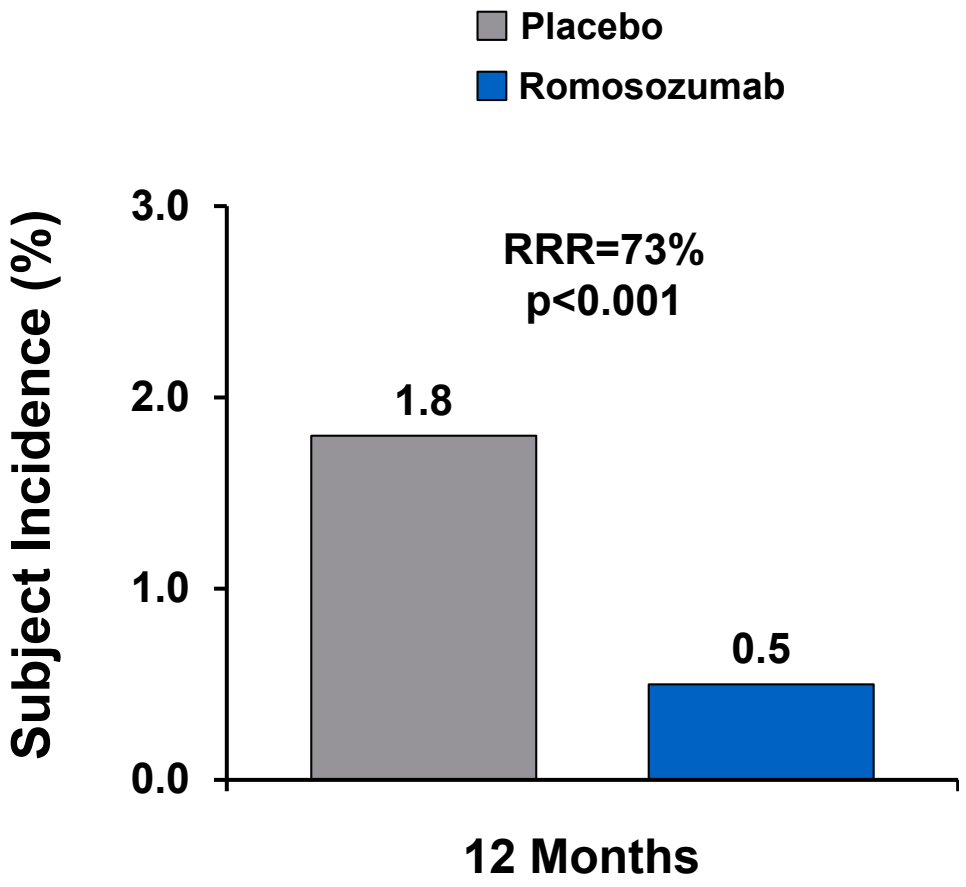
Exploratory Endpoints:

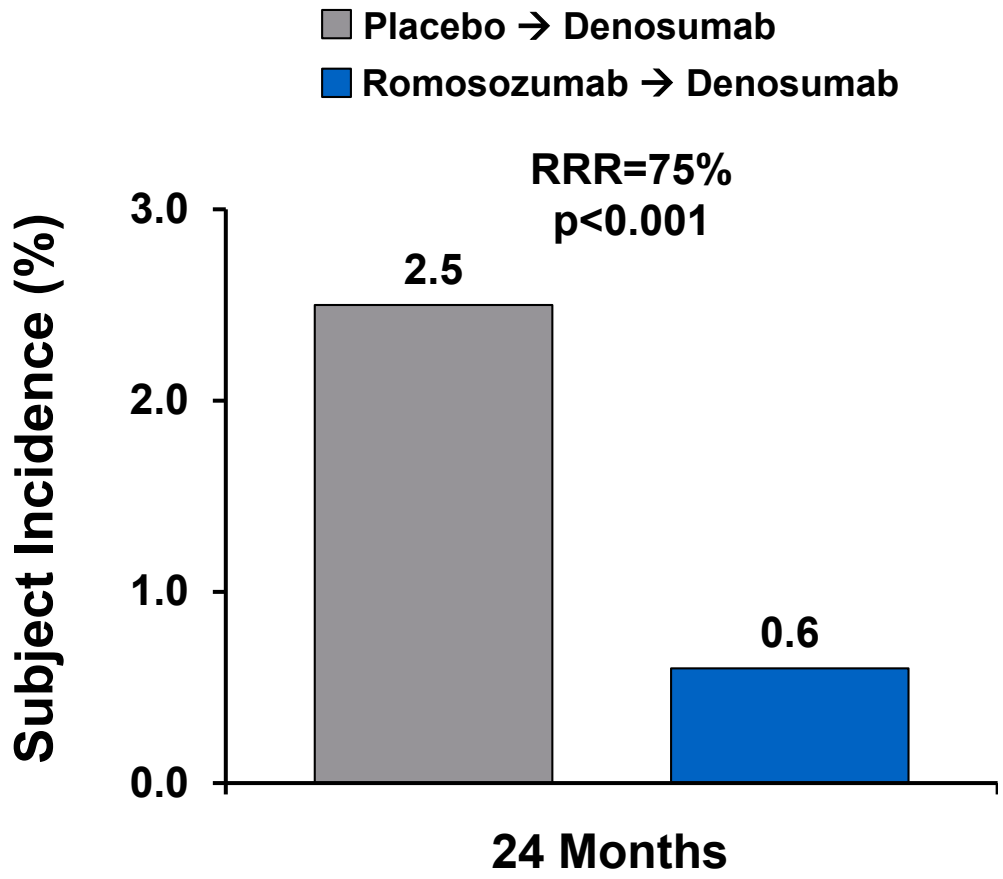
- Clinical, non-vertebral, and other fracture categories at 36 months

Study 337: Baseline Characteristics and Study Disposition

Baseline Characteristic	Placebo N=3591	Romosozumab N=3589
Age in years, mean (SD)	70.8 (6.9)	70.9 (7.0)
≥75 years of age, %	31.2	31.2
Prevalent vertebral fracture, %	18.0	18.7
Lumbar spine BMD T-score, mean (SD)	-2.71 (1.04)	-2.72 (1.04)
Total hip BMD T-score, mean (SD)	-2.46 (0.47)	-2.48 (0.47)
Study completers, %		
Completed 12 months	89.3	88.7
Completed 24 months	84.4	83.4
Completed 36 months	80.5	79.4

Study 337: Co-primary Endpoints of New Vertebral Fracture at 12 and 24 Months





RRR=relative risk reduction.

Phase 3 Clinical Studies in Postmenopausal Women with Osteoporosis

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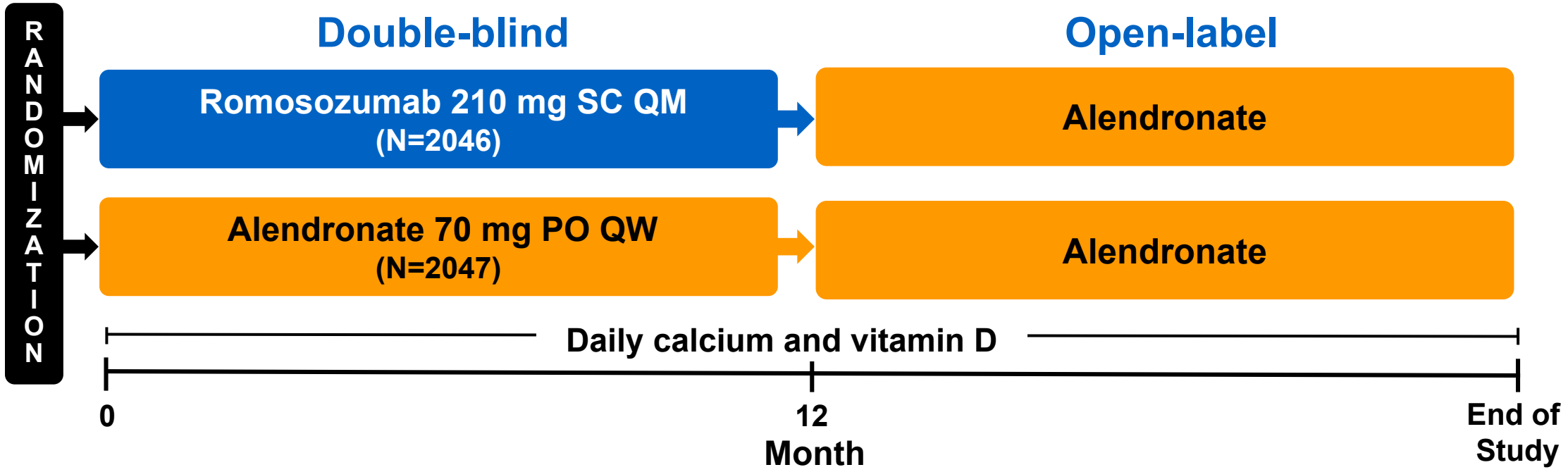
289	436	Teriparatide	–	12 months	▪ Percent change total hip BMD through 12 months

[a]Primary analysis was event-driven and occurred at a median follow-up of 33 (Q1, Q3: 27, 40) months.

Study 142: Study Design



Key Inclusion Criteria:

- BMD T-score ≤ -2.5 at total hip or femoral neck, and
  - At least 1 moderate or severe vertebral fractures *or*
  - At least 2 mild vertebral fractures
- BMD T-score ≤ -2.0 at total hip or femoral neck, and
  - At least 2 moderate or severe vertebral fractures or
  - Hip fracture sustained 3–24 months prior to randomization

Primary Endpoints:

- New vertebral fracture at 24 months
- Clinical fracture at Primary Analysis[a]

Key Secondary Endpoints:

- Non-vertebral fracture at Primary Analysis[a]
- BMD at lumbar spine, total hip, and femoral neck at 12 and 24 months

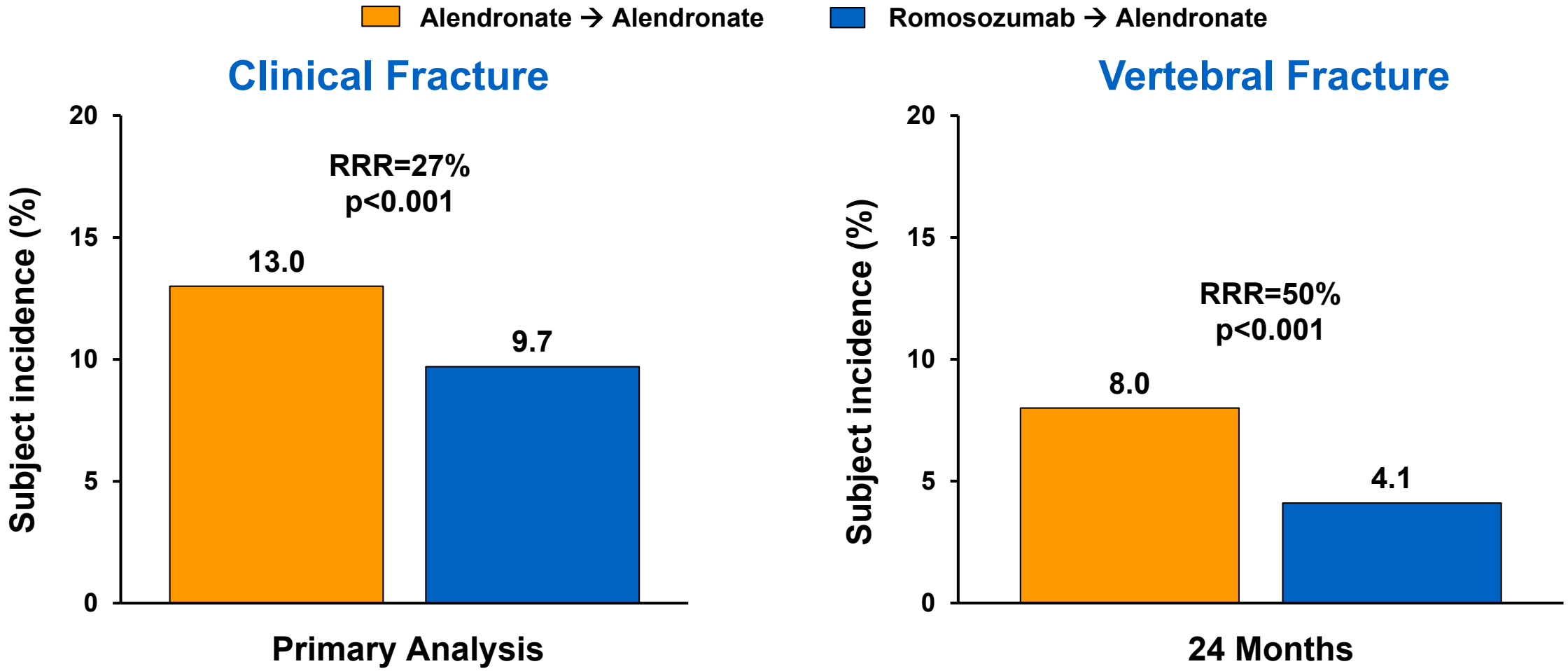
[a]Primary analysis occurred after all subjects completed 24 month visit and clinical fracture confirmed in >330 subjects.

Study 142: Baseline Characteristics and Study Disposition

Baseline Characteristic	Alendronate N=2047	Romosozumab N=2046
Age in years, mean (SD)	74.2 (7.5)	74.4 (7.5)
≥75 years of age, %	52.3	52.4
Prevalent vertebral fracture, %	95.9	96.2
Previous hip fracture, %	8.7	8.6
Lumbar spine BMD T-score, mean (SD)	-2.99 (1.24)	-2.94 (1.25)
Total hip BMD T-score, mean (SD)	-2.81 (0.67)	-2.78 (0.68)
Study completers, %		
Completed 12 months	89.1	89.5
Completed Primary Analysis Period[a]	77.0	76.9

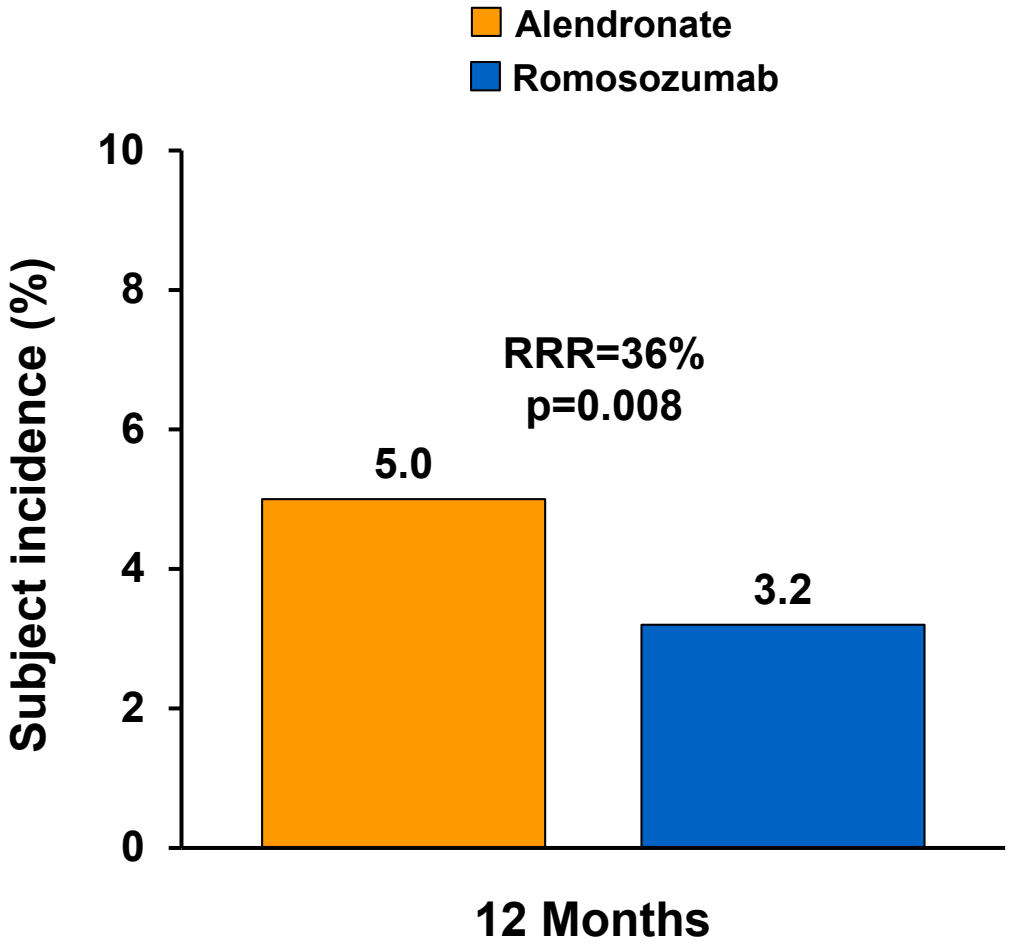
[a]Median follow-up of 33 (IQR 27-40) months; IQR = interquartile range.

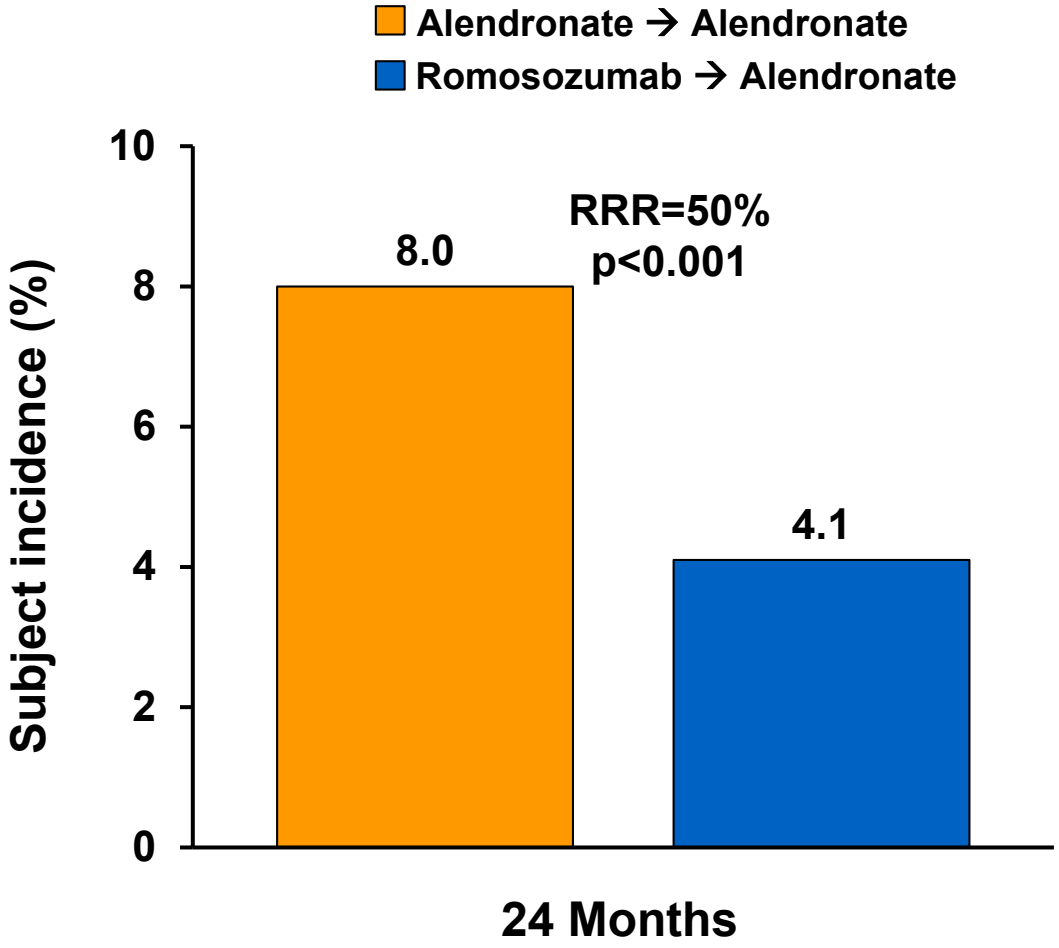
Study 142: Primary Endpoints of Clinical Fracture at Primary Analysis and Vertebral Fracture at 24 Months



RRR=relative risk reduction.

Study 142: Effect of 12 Months of Romosozumab Followed by Alendronate on Vertebral Fracture





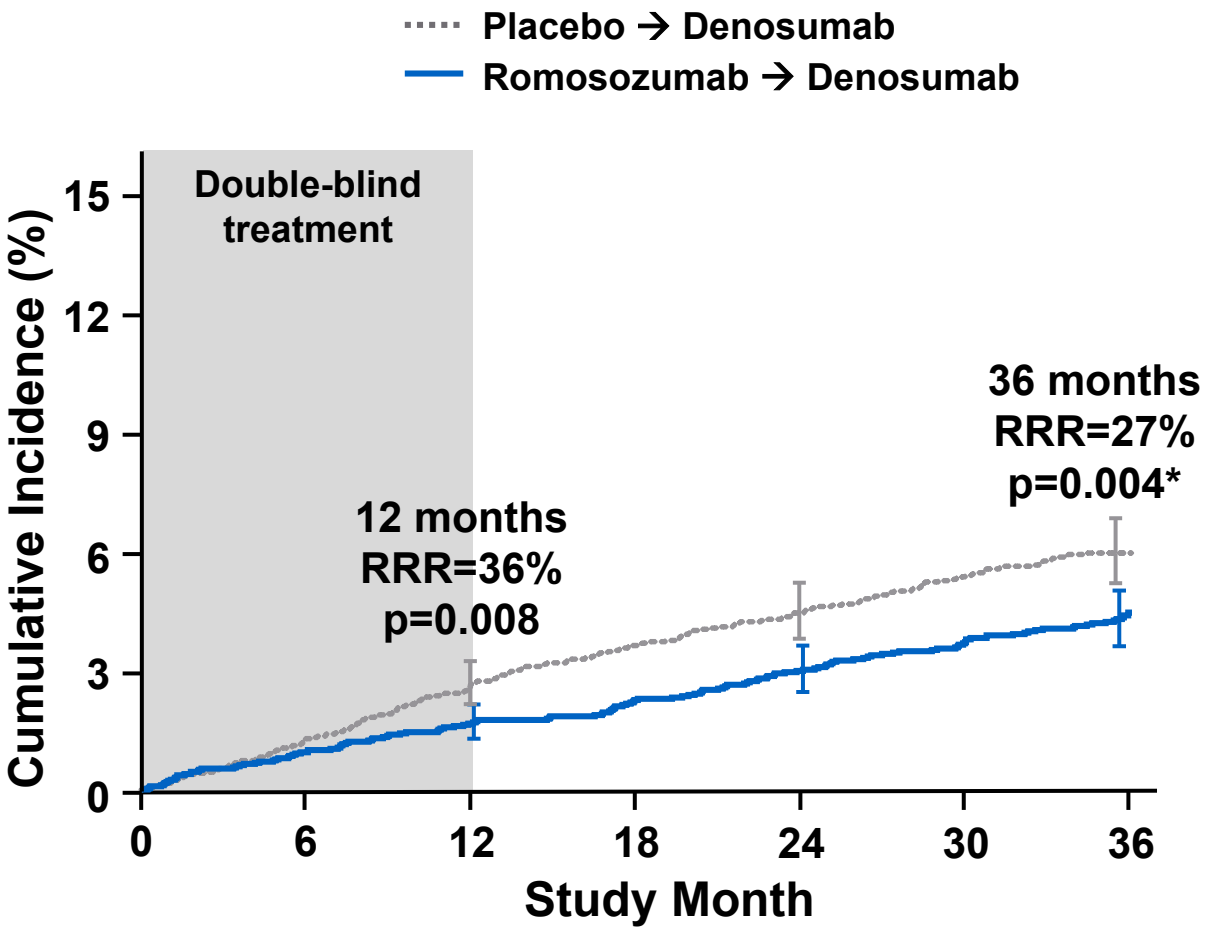
p-value at 12 months is nominal, without multiplicity adjustment.

Studies 337 and 142: Time to Event Analyses

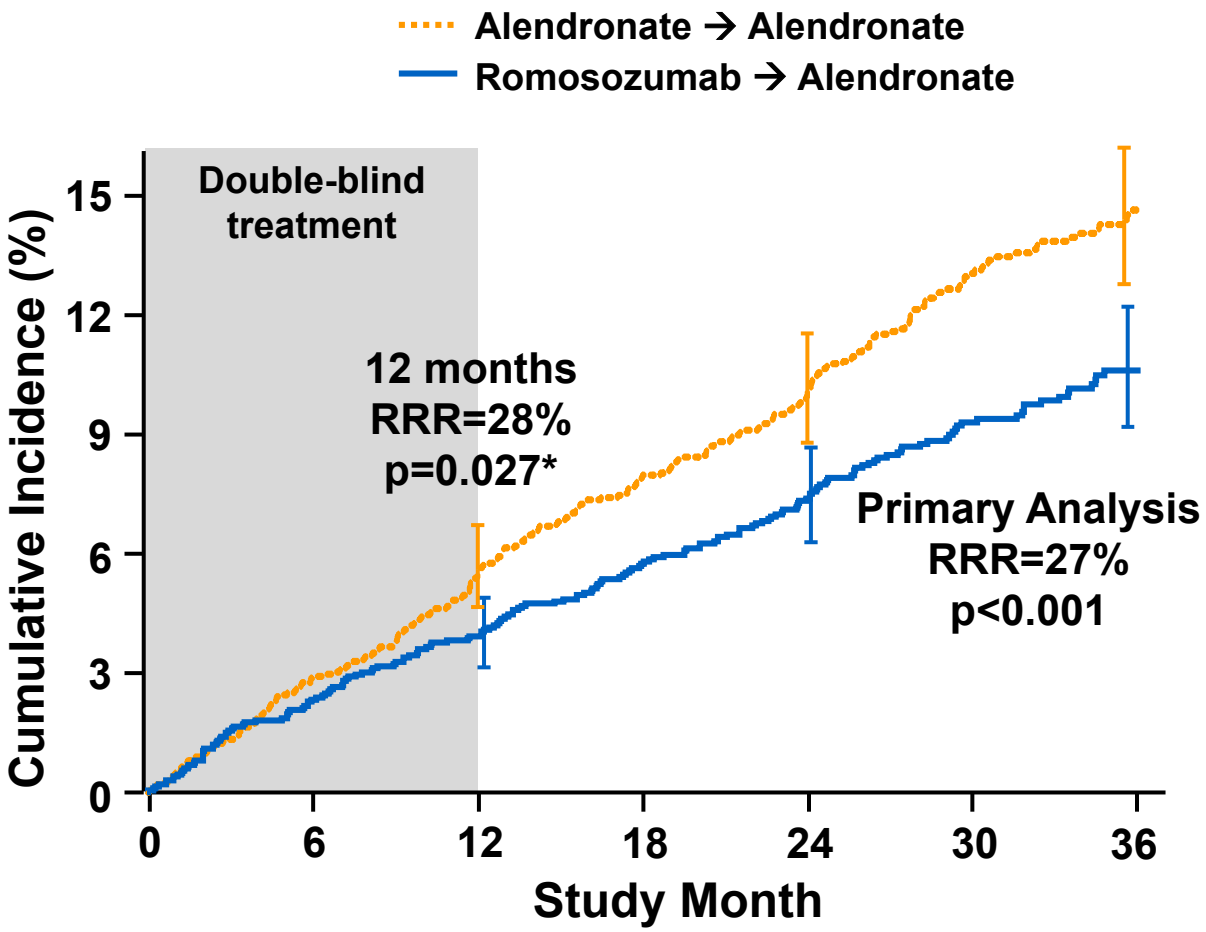
- Clinical Fractures
- Hip Fractures

Studies 337 and 142: Time to First Clinical Fracture

Study 337



Study 142



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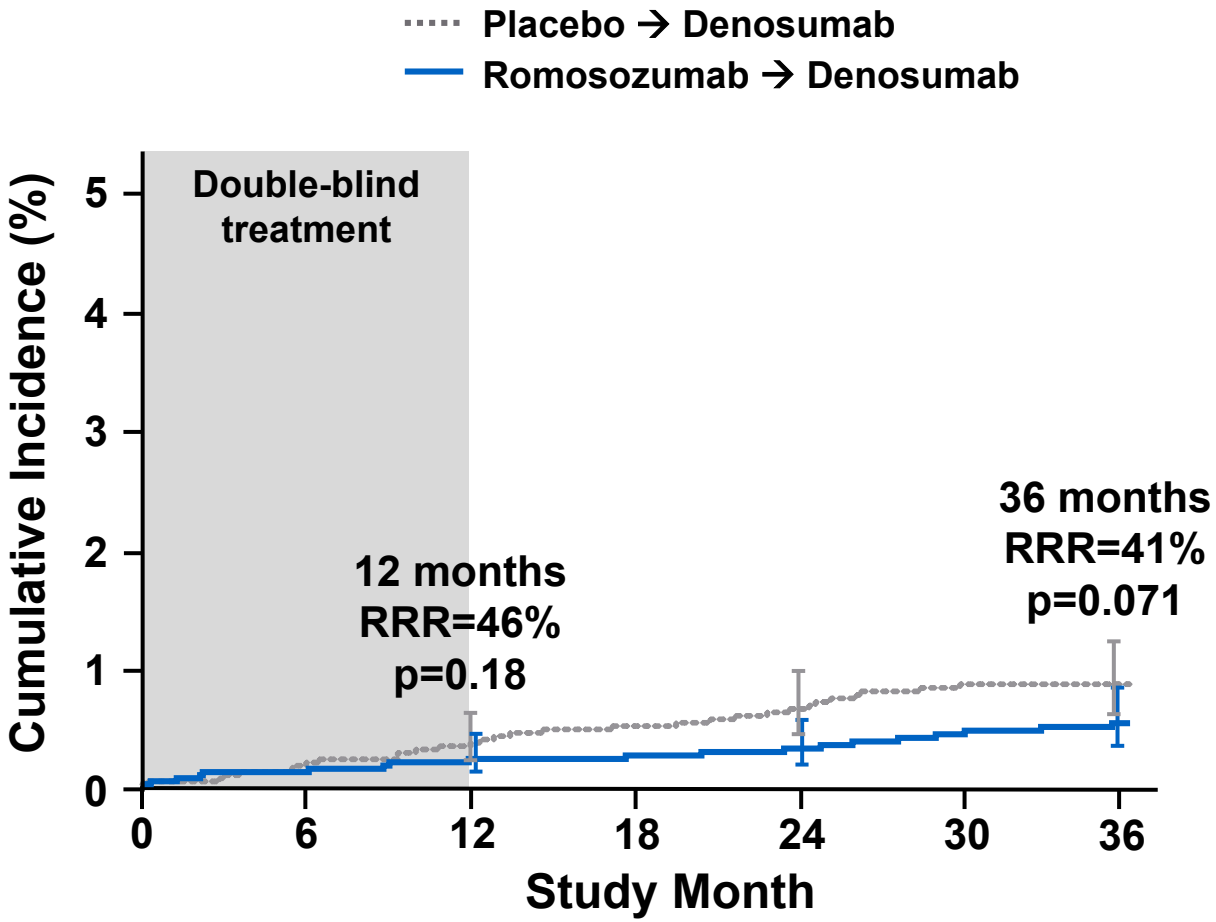
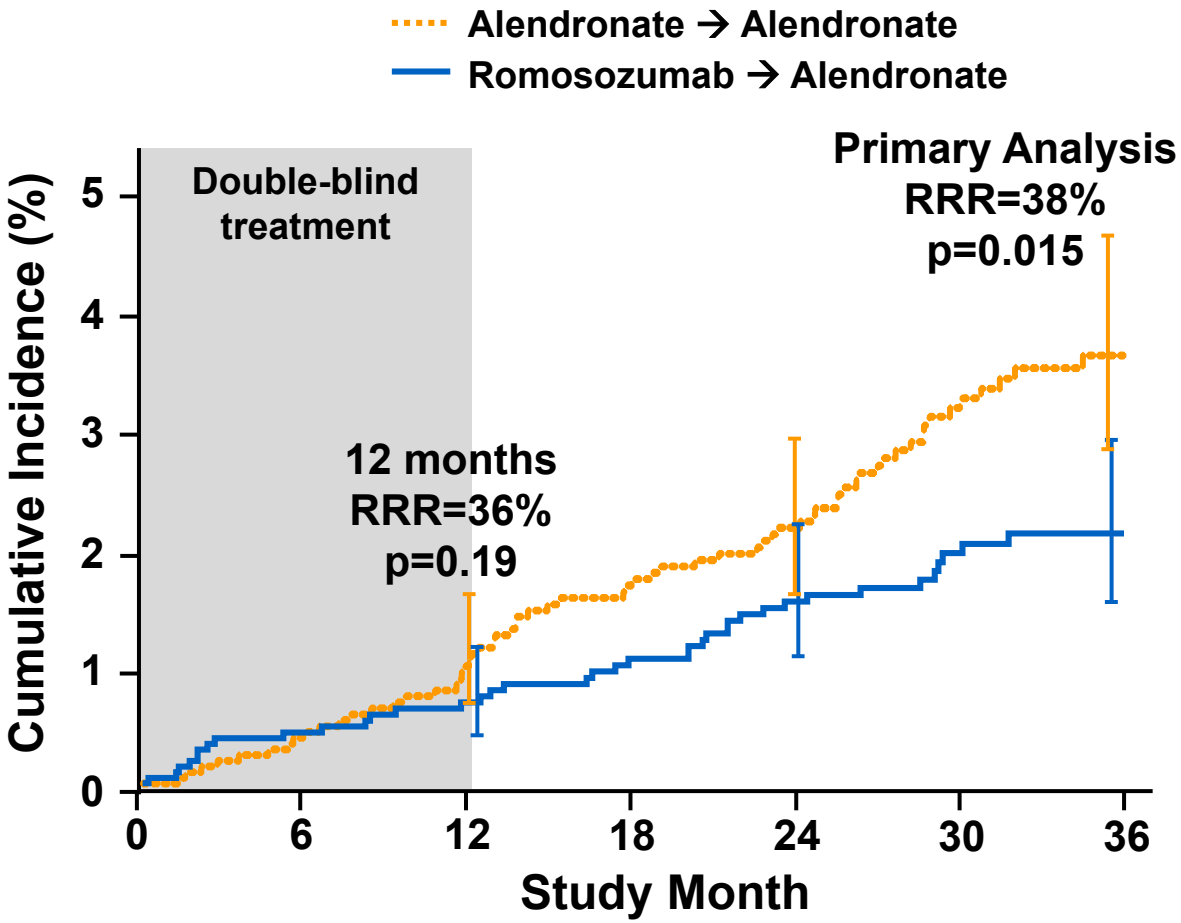
Studies 337 and 142: Time to First Hip Fracture

Study 337



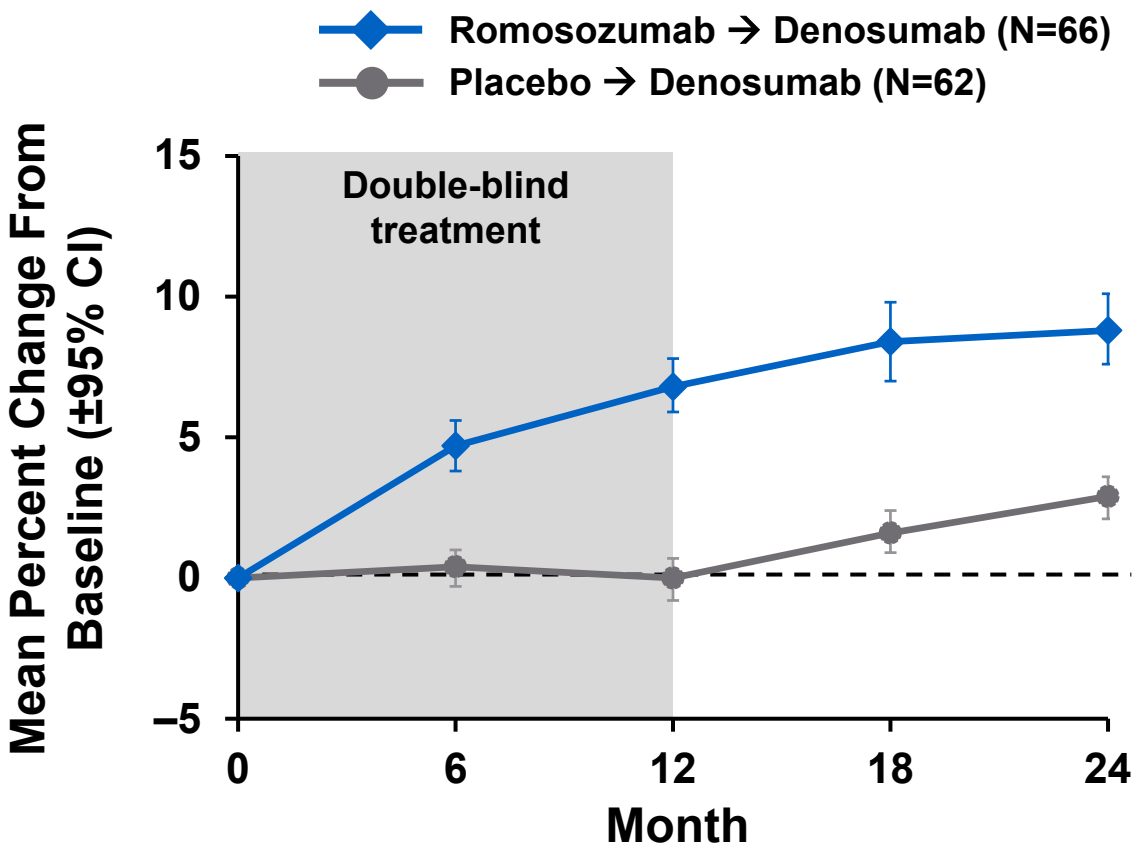
Study 142



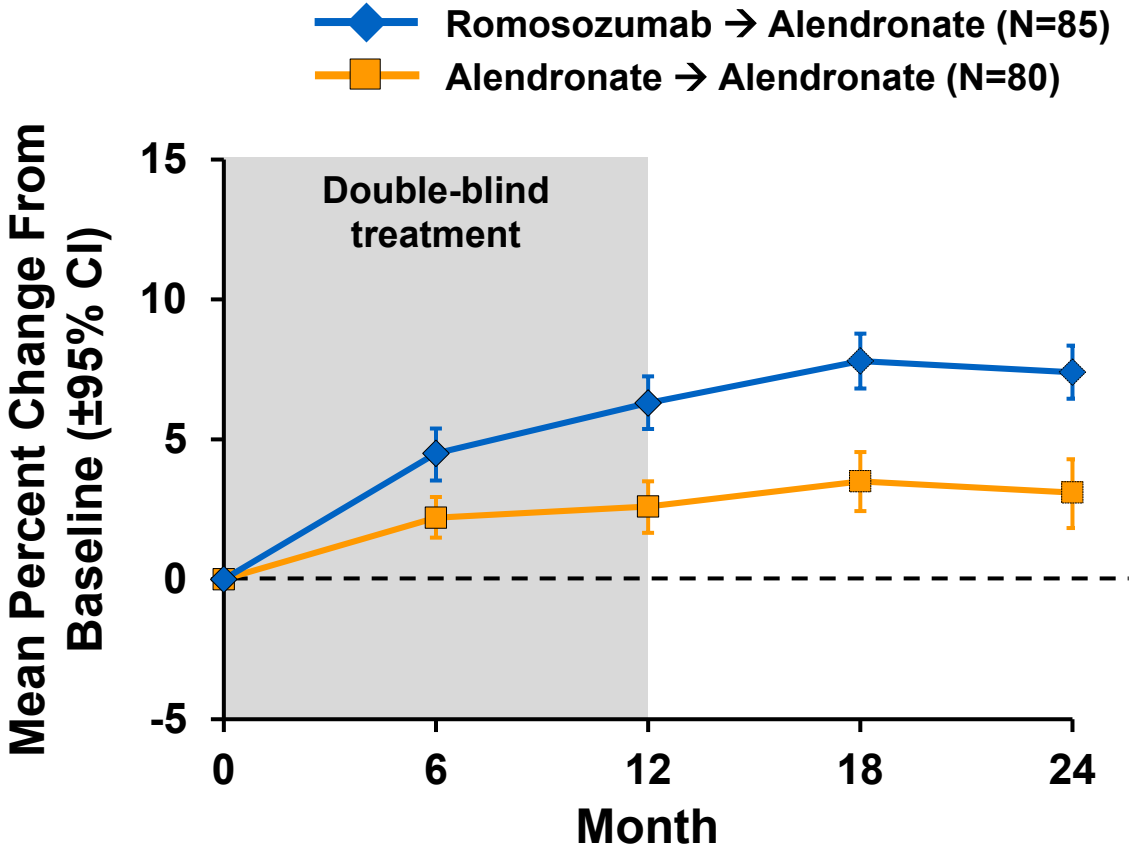
* p-value is nominal, without multiplicity adjustment.

Studies 337 and 142 DXA Sub-study: Change in Bone Mineral Density at Total Hip Through 24 Months

Study 337



Study 142



P<0.001 at all timepoints are nominal, without multiplicity adjustment

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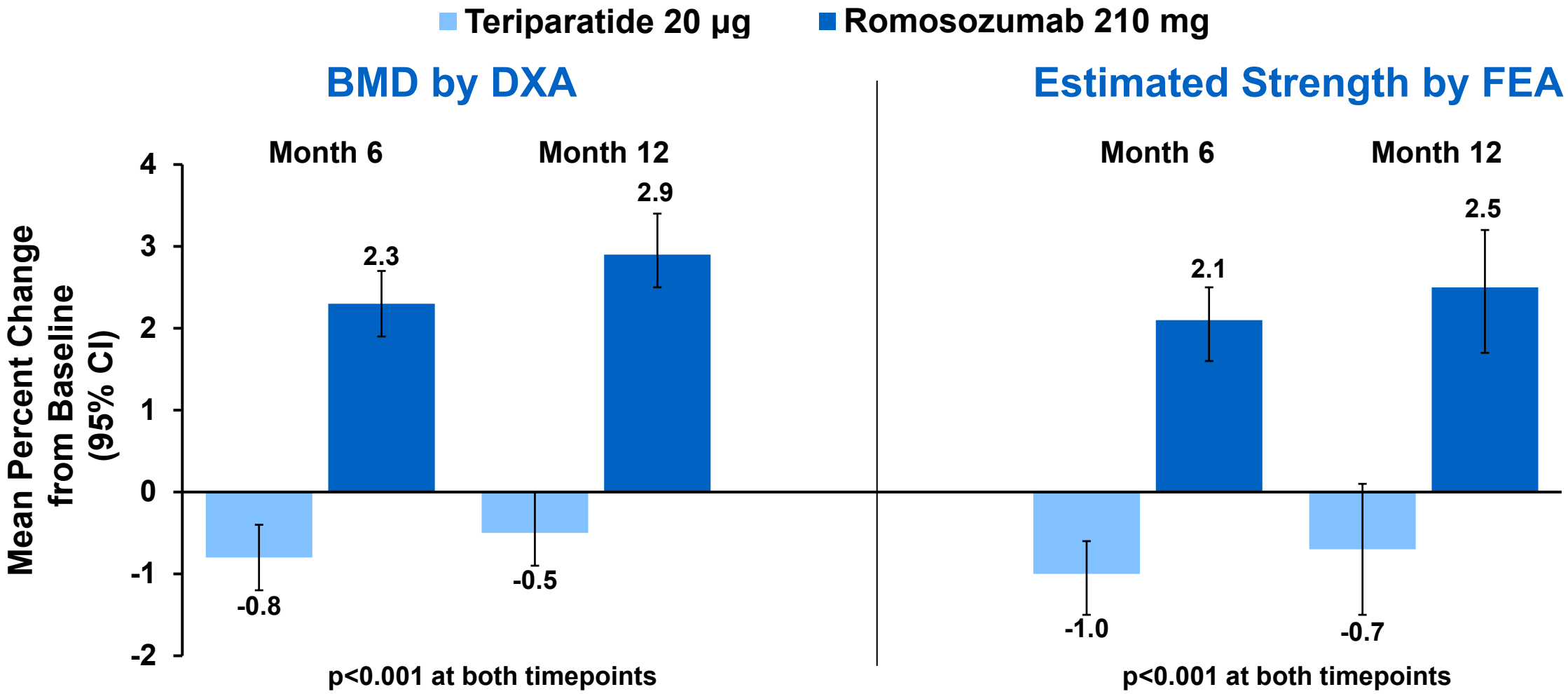
Study 289: Total Hip Bone Mineral Density and Estimated Strength by Finite Element Analysis



FEA, Finite Element Analysis. Langdahl B et al. *Lancet.* 2017; 390:1585–94.

Clinical Efficacy Summary

- **Significant advancement in therapy**
- **Rapid and substantial gains in BMD vs standard of care therapies**
  - More than 2.5x greater than alendronate
  - More than 1.5x greater than teriparatide
- **Rates of fracture reduced across the skeleton over alendronate**
  - 50% vertebral fracture reduction
  - 38% hip fracture reduction
- **Benefit with romosozumab maintained with sequential antiresorptive therapy**

Presentation Overview

Introduction	**Scott Wasserman, MD** Vice President, Global Development, Amgen
Unmet Medical Need	**Michael McClung, MD** Founding Director, Oregon Osteoporosis Center
Clinical Efficacy	**Rachel Wagman, MD** Executive Medical Director, Global Development, Amgen
Safety and Benefit/Risk	**Scott Wasserman, MD** Vice President, Global Development, Amgen
Amgen Conclusion	**Steven Galson, MD, MPH** Senior Vice President, Global Regulatory Affairs and Safety, Amgen
Clinician Perspective	**Felicia Cosman, MD** Professor of Medicine, Columbia University

Safety

Scott Wasserman, MD

Vice President, Global Development

Amgen Inc.

Safety Outline

- Exposure
- Summary of Adverse Events
- Key Events of Interest
- Cardiovascular Safety

Exposure

- **Overall safety database**
  - ~14,000 subjects
    - 7518 received ≥1 dose of romosozumab
- **Studies 337 and 142**
  - ~11,000 subjects (~7000 in Study 337; ~4000 in Study 142)
    - 5621 subjects received romosozumab

Summary of Adverse Events

	Subject incidence			
	Study 337		Study 142	
	Placebo N=3576 %	Romosozumab N=3581 %	Alendronate N=2014 %	Romosozumab N=2040 %
12-month Double-blind Treatment Period				
All treatment emergent adverse events	80.1	78.5	78.6	75.6
Leading to study drug discontinuation	2.7	3.0	3.3	3.5
Leading to study discontinuation	1.4	1.3	1.3	1.4
Serious adverse events (SAE)	8.8	9.6	13.8	12.8

Hypersensitivity and Hypocalcemia

	Subject incidence			
	Study 337		Study 142	
	Placebo N=3576 n (%)	Romosozumab N=3581 n (%)	Alendronate N=2014 n (%)	Romosozumab N=2040 n (%)
12-month Double-blind Treatment Period				
Hypersensitivity	247 (6.9)	242 (6.8)	118 (5.9)	122 (6.0)
Serious Adverse Event	0	6 (0.2)	2 (<0.1)	3 (0.1)
Hypocalcemia	0	1 (<0.1)	1 (<0.1)	1 (<0.1)
Serious Adverse Event	0	0	0	0

Osteonecrosis of the Jaw and Atypical Femoral Fracture

	Subject incidence			
	Study 337		Study 142	
	Placebo N=3576 n (%)	Romosozumab N=3581 n (%)	Alendronate N=2014 n (%)	Romosozumab N=2040 n (%)
12-month Double-blind Treatment Period				
Osteonecrosis of the jaw (ONJ)	0	1 (<0.1)	0	0
Atypical femoral fracture (AFF)	0	1 (<0.1)	0	0
Overall Study Period				
Osteonecrosis of the jaw (ONJ)	0	2 (<0.1)	1 (<0.1)	2 (0.1)
Atypical femoral fracture (AFF)	0	1 (<0.1)	4 (0.2)	3 (0.1)

Osteonecrosis of the jaw and atypical femoral fracture were adjudicated.

Cardiovascular Safety

Cardiovascular Safety Overview

- Study overview and analysis periods
- Adjudication process
- Cardiovascular safety in Study 337, Study 142, and meta-analysis
- Genetic, clinical and non-clinical data
- Conclusion

Phase 3 Postmenopausal Osteoporosis with CV Serious Adverse Event Adjudication

Study Number	Number of Subjects	Treatment Sequence		Study Duration	Primary Endpoints
		Double-blind Comparator	Follow-on Therapy		
337	7180	Placebo	Denosumab	36 months	▪ New vertebral fracture at 12 and 24 months
142	4093	Alendronate	Alendronate	▪ Clinical fracture event driven; ▪ 36 months median (IQR: 30, 43)	▪ New vertebral fracture at 24 months ▪ Clinical fracture at the Primary Analysis

Phase 3 Postmenopausal Osteoporosis with CV Serious Adverse Event Adjudication

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12-month period

Phase 3 Postmenopausal Osteoporosis with CV Serious Adverse Event Adjudication

Study Number	Number of Subjects	Treatment Sequence		Study Duration	Primary Endpoints
		Double-blind Comparator	Follow-on Therapy		
337	7180	Placebo	Denosumab	36 months	▪ New vertebral fracture at 12 and 24 months
142	4093	Alendronate	Alendronate	▪ Clinical fracture event driven; ▪ 36 months median (IQR; 30, 43)	▪ New vertebral fracture at 24 months ▪ Clinical fracture at the Primary Analysis

Overall study period

Cardiovascular-related Baseline Characteristics

Characteristic, %	Study 337		Study 142	
	Placebo N=3576	Romosozumab N=3581	Alendronate N=2014	Romosozumab N=2040
Mean age, years (SD)	**70.8 (6.9)**	**70.9 (7.0)**	**74.2 (7.5)**	**74.4 (7.5)**
Current / former smoker	29.0	27.4	29.3	26.1
Hypercholesterolemia	39.4	38.5	33.5	34.8
Hypertension	**53.7**	**52.8**	**60.9**	**61.2**
Diabetes	13.2	12.6	13.7	12.0
Cerebrovascular cond.	**5.5**	**5.0**	**9.2**	**7.3**
Stroke	**2.7**	**2.3**	**4.0**	**2.8**
Ischemic heart disease	**9.6**	**8.9**	**12.8**	**14.5**
Myocardial infarction	**2.2**	**2.1**	**2.5**	**3.5**
Heart failure	**2.5**	**2.1**	**4.0**	**3.5**
Atrial fibrillation	**2.1**	**1.6**	**3.7**	**4.5**

Cardiovascular-related Baseline Medications

Characteristic	Study 337		Study 142	
	Placebo N=3576	Romosozumab N=3581	Alendronate N=2014	Romosozumab N=2040
Subjects with cardiovascular-related baseline medications	**57.7**	**56.4**	**61.5**	**61.5**
Beta-Blockers	**20.4**	**20.0**	**23.7**	**25.4**
ACE Inhibitors	**19.6**	**20.4**	**24.3**	**26.1**
Angiotensin II receptor antagonists	16.8	16.1	18.6	17.0
Statins	26.4	25.5	23.6	24.4
Antithrombotic	**22.8**	**23.4**	**27.8**	**28.3**
Warfarin	1.8	1.0	3.5	3.7
Anti-platelet therapy	21.1	22.4	23.5	23.7
Aspirin	19.9	21.0	21.7	22.0
Insulin	1.8	1.6	2.7	2.0
Non-insulin Glycemic Control Medications	8.5	8.1	7.9	7.5

Phase 3 Cardiovascular Risk Assessment: Adjudication Process

Cardiovascular Serious Adverse Event (SAE)-based Adjudication

Study 337
(N = 7180)

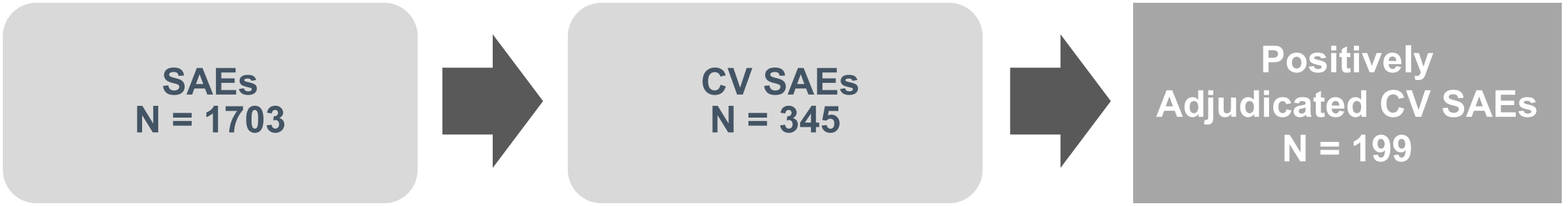
Study 142
(N = 4093)

- Identification of potential CV SAEs from clinical trial database
- Prospective, independent, treatment-blinded adjudication by DCRI using CDISC definitions

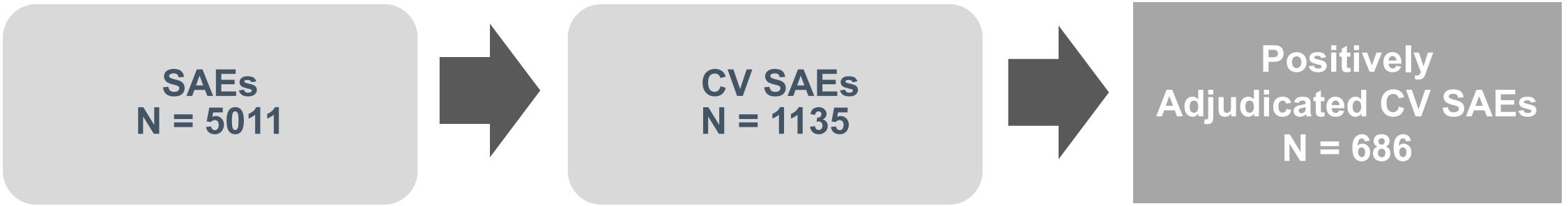
CDISC, Clinical Data Interchange Standards Consortium

Phase 3 Cardiovascular Risk Assessment: Adjudication Process Results

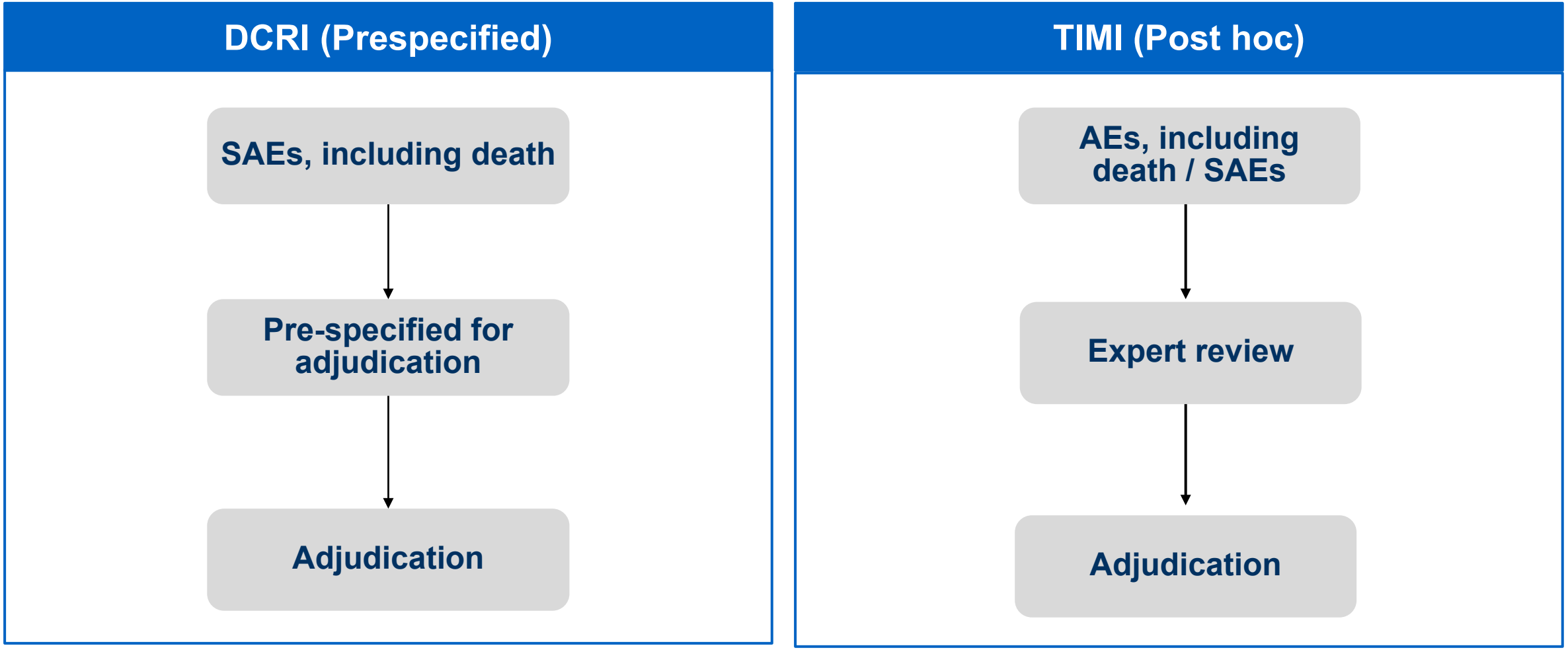
12-month Period



Overall Study Period



Cardiovascular Event Adjudication Process



Subject Incidences

12-month and Overall Study Periods

Subject Incidence of Positively Adjudicated CV SAEs in 12-month Double-blind Period

Category Subcategory	Subject Incidence			
	Study 337		Study 142	
	Placebo N=3576 n (%)	Romosozumab N=3581 n (%)	Alendronate N=2014 n (%)	Romosozumab N=2040 n (%)
Positively Adjudicated CV SAE	**46 (1.3)**	**46 (1.3)**	**38 (1.9)**	**50 (2.5)**
MACE	29 (0.8)	30 (0.8)	22 (1.1)	41 (2.0)
Cardiac ischemic event	16 (0.4)	16 (0.4)	6 (0.3)	16 (0.8)
Myocardial infarction	8 (0.2)	9 (0.3)	5 (0.2)	16 (0.8)
Cerebrovascular event	11 (0.3)	10 (0.3)	7 (0.3)	16 (0.8)
Stroke	10 (0.3)	8 (0.2)	7 (0.3)	13 (0.6)
All-cause death	24 (0.7)	29 (0.8)	22 (1.1)	30 (1.5)
Cardiovascular death	15 (0.4)	17 (0.5)	12 (0.6)	17 (0.8)
Heart failure	5 (0.1)	7 (0.2)	8 (0.4)	4 (0.2)
Noncoronary revascularization	2 (<0.1)	1 (<0.1)	5 (0.2)	3 (0.1)
Peripheral vascular ischemic event not requiring revascularization	1 (<0.1)	4 (0.1)	2 (<0.1)	0

Subject Incidence of Positively Adjudicated CV SAEs in 12-month Double-blind Period

Category Subcategory	Subject Incidence			
	Study 337		Study 142	
	Placebo N=3576 n (%)	Romosozumab N=3581 n (%)	Alendronate N=2014 n (%)	Romosozumab N=2040 n (%)
Positively adjudicated CV SAE	46 (1.3)	46 (1.3)	38 (1.9)	50 (2.5)
MACE	**29 (0.8)**	**30 (0.8)**	**22 (1.1)**	**41 (2.0)**
Cardiac ischemic event	16 (0.4)	16 (0.4)	6 (0.3)	16 (0.8)
Myocardial infarction	8 (0.2)	9 (0.3)	5 (0.2)	16 (0.8)
Cerebrovascular event	11 (0.3)	10 (0.3)	7 (0.3)	16 (0.8)
Stroke	10 (0.3)	8 (0.2)	7 (0.3)	13 (0.6)
All-cause death	24 (0.7)	29 (0.8)	22 (1.1)	30 (1.5)
Cardiovascular death	15 (0.4)	17 (0.5)	12 (0.6)	17 (0.8)
Heart failure	5 (0.1)	7 (0.2)	8 (0.4)	4 (0.2)
Noncoronary revascularization	2 (<0.1)	1 (<0.1)	5 (0.2)	3 (0.1)
Peripheral vascular ischemic event not requiring revascularization	1 (<0.1)	4 (0.1)	2 (<0.1)	0

Subject Incidence of Positively Adjudicated CV SAEs in the Overall Study Period

Category Subcategory	Subject Incidence			
	Study 337		Study 142	
	Placebo N=3576 n (%)	Romosozumab N=3581 n (%)	Alendronate N=2014 n (%)	Romosozumab N=2040 n (%)
Positively adjudicated CV SAE	**124 (3.5)**	**128 (3.6)**	**137 (6.8)**	**144 (7.1)**
MACE	86 (2.4)	95 (2.7)	102 (5.1)	117 (5.7)
Cardiac ischemic event	38 (1.1)	36 (1.0)	25 (1.2)	32 (1.6)
Myocardial infarction	19 (0.5)	23 (0.6)	21 (1.0)	23 (1.1)
Cerebrovascular event	36 (1.0)	43 (1.2)	27 (1.3)	47 (2.3)
Stroke	31 (0.9)	37 (1.0)	24 (1.2)	42 (2.1)
All-cause death	85 (2.4)	72 (2.0)	103 (5.1)	101 (5.0)
Cardiovascular death	50 (1.4)	43 (1.2)	68 (3.4)	67 (3.3)
Heart failure	15 (0.4)	12 (0.3)	25 (1.2)	14 (0.7)
Noncoronary revascularization	4 (0.1)	2 (<0.1)	10 (0.5)	7 (0.3)
Peripheral vascular ischemic event not requiring revascularization	3 (<0.1)	8 (0.2)	5 (0.2)	2 (<0.1)

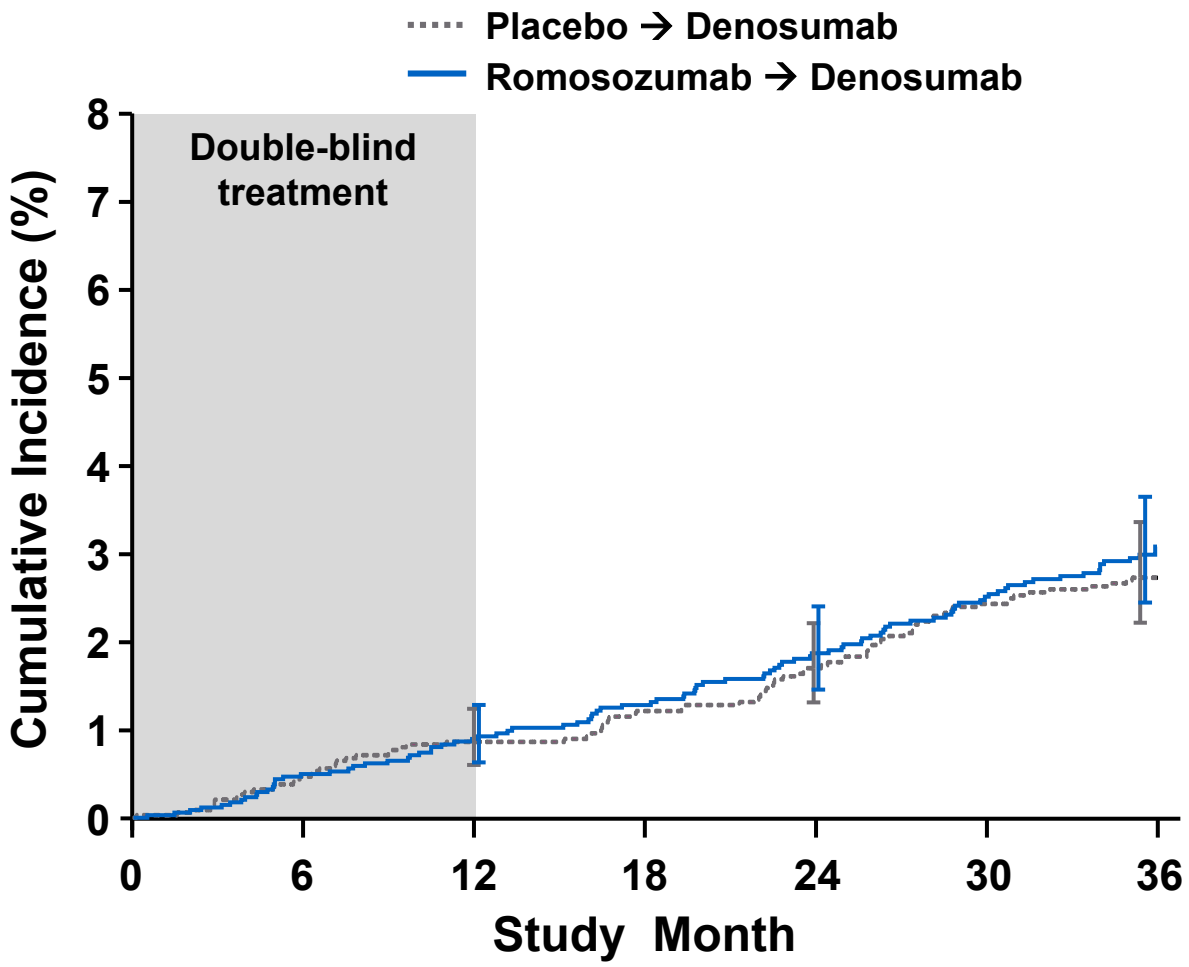
Subject Incidence of Positively Adjudicated CV SAEs in the Overall Study Period

Category Subcategory	Subject Incidence			
	Study 337		Study 142	
	Placebo N=3576 n (%)	Romosozumab N=3581 n (%)	Alendronate N=2014 n (%)	Romosozumab N=2040 n (%)
Positively adjudicated CV SAE	124 (3.5)	128 (3.6)	137 (6.8)	144 (7.1)
MACE	**86 (2.4)**	**95 (2.7)**	**102 (5.1)**	**117 (5.7)**
Cardiac ischemic event	38 (1.1)	36 (1.0)	25 (1.2)	32 (1.6)
Myocardial infarction	19 (0.5)	23 (0.6)	21 (1.0)	23 (1.1)
Cerebrovascular event	36 (1.0)	43 (1.2)	27 (1.3)	47 (2.3)
Stroke	31 (0.9)	37 (1.0)	24 (1.2)	42 (2.1)
All-cause death	85 (2.4)	72 (2.0)	103 (5.1)	101 (5.0)
Cardiovascular death	50 (1.4)	43 (1.2)	68 (3.4)	67 (3.3)
Heart failure	15 (0.4)	12 (0.3)	25 (1.2)	14 (0.7)
Noncoronary revascularization	4 (0.1)	2 (<0.1)	10 (0.5)	7 (0.3)
Peripheral vascular ischemic event not requiring revascularization	3 (<0.1)	8 (0.2)	5 (0.2)	2 (<0.1)

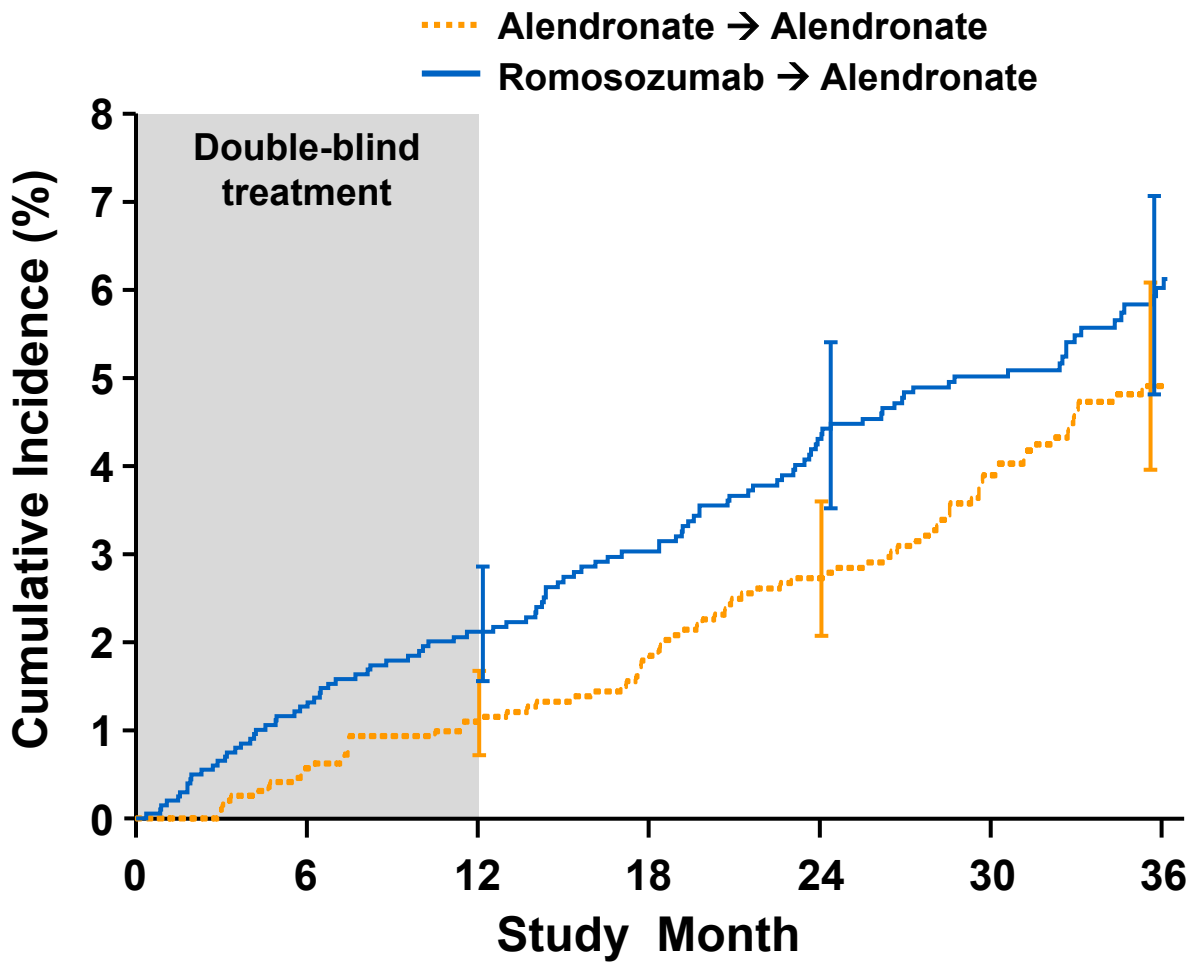
Time to Event Analyses

Studies 337 and 142: Time to First Positively Adjudicated MACE

Study 337

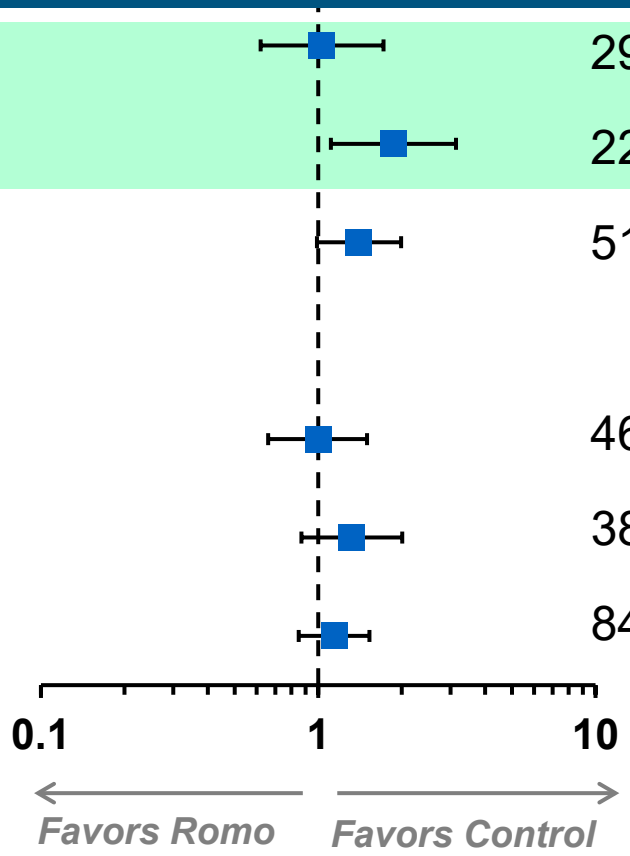


Study 142



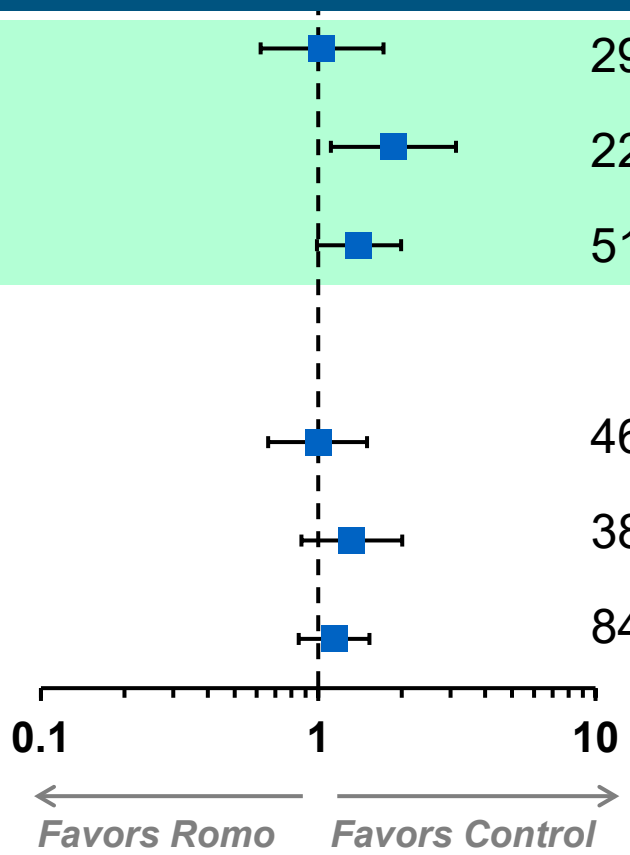
Time to MACE and Positively Adjudicated CV SAE in 12-month Period

	Study	Control N=5590 n (%)	Romo N=5621 n (%)	HR	95% CI
MACE	337	29 (0.8)	30 (0.8)	1.03	(0.62, 1.72)
	142	22 (1.1)	41 (2.0)	1.87	(1.11, 3.14)
	Meta	51 (0.9)	71 (1.3)	1.39	(0.97, 2.00)
CV SAE	337	46 (1.3)	46 (1.3)	1.00	(0.66, 1.50)
	142	38 (1.9)	50 (2.5)	1.32	(0.87, 2.01)
	Meta	84 (1.5)	96 (1.7)	1.14	(0.85, 1.53)



Time to MACE and Positively Adjudicated CV SAE in 12-month Period

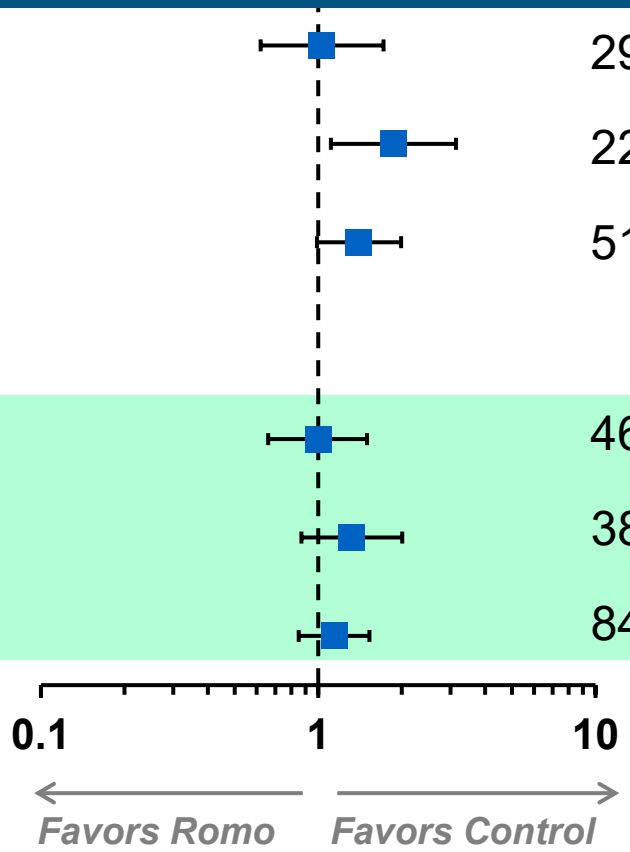
	Study	Control N=5590 n (%)	Romo N=5621 n (%)	HR	95% CI
MACE	337	29 (0.8)	30 (0.8)	1.03	(0.62, 1.72)
	142	22 (1.1)	41 (2.0)	1.87	(1.11, 3.14)
	Meta	51 (0.9)	71 (1.3)	1.39	(0.97, 2.00)
CV SAE	337	46 (1.3)	46 (1.3)	1.00	(
	142	38 (1.9)	50 (2.5)	1.32	(0.87, 2.01)
	Meta	84 (1.5)	96 (1.7)	1.14	(0.85, 1.53)



HR 1.40 (0.99, 1.99)
for meta-analysis of
Studies 337, 142, and 174

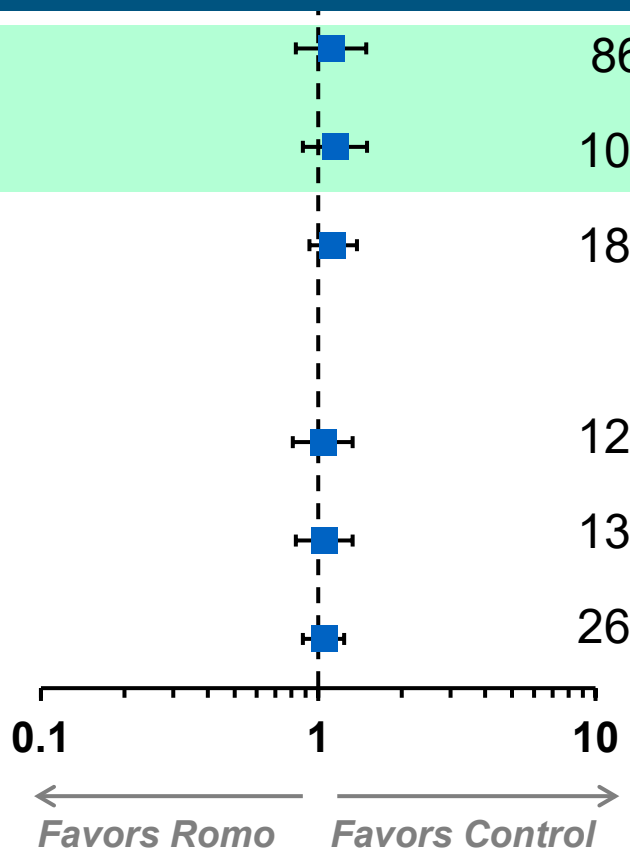
Time to MACE and Positively Adjudicated CV SAE in 12-month Period

	Study	Control N=5590 n (%)	Romo N=5621 n (%)	HR	95% CI
MACE	337	29 (0.8)	30 (0.8)	1.03	(0.62, 1.72)
	142	22 (1.1)	41 (2.0)	1.87	(1.11, 3.14)
	Meta	51 (0.9)	71 (1.3)	1.39	(0.97, 2.00)
CV SAE	337	46 (1.3)	46 (1.3)	1.00	(0.66, 1.50)
	142	38 (1.9)	50 (2.5)	1.32	(0.87, 2.01)
	Meta	84 (1.5)	96 (1.7)	1.14	(0.85, 1.53)



Time to MACE and Positively Adjudicated CV SAE in Overall Study Period

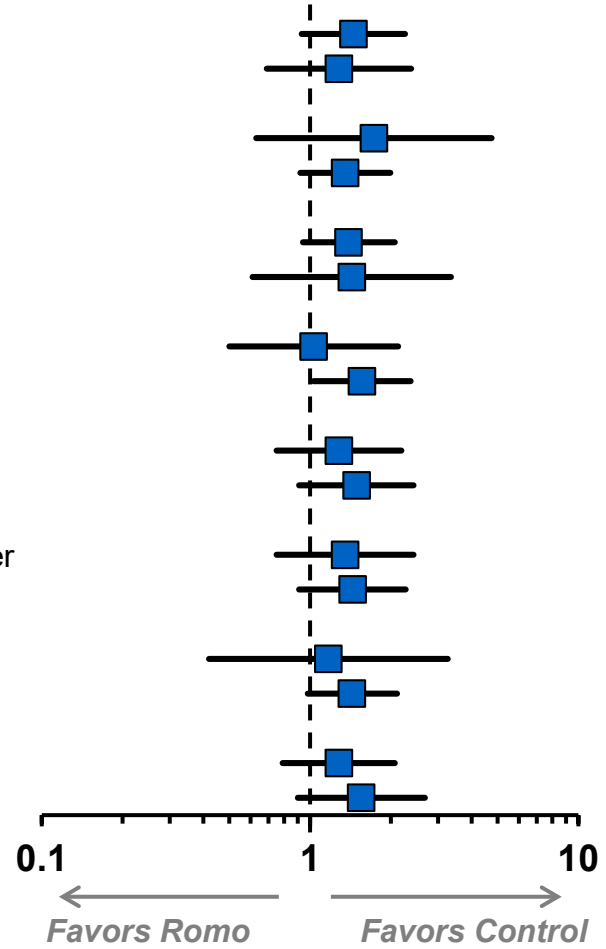
	Study	Control N=5590 n (%)	Romo N=5621 n (%)	HR	95% CI
MACE	337	86 (2.4)	95 (2.7)	1.12	(0.83, 1.49)
	142	102 (5.1)	117 (5.7)	1.15	(0.88, 1.50)
	Meta	188 (3.4)	212 (3.8)	1.13	(0.93, 1.38)
CV SAE	337	124 (3.5)	128 (3.6)	1.04	(0.81, 1.33)
	142	137 (6.8)	144 (7.1)	1.05	(0.83, 1.33)
	Meta	261 (4.7)	272 (4.8)	1.05	(0.88, 1.24)



Meta-analysis (Studies 337 and 142): Evaluation of Cardiovascular Risk Subgroups Based on MACE

12-month Period

Category		Control N=5590 n/N1 (%)	Treatment N=5621 n/N1 (%)	HR	95% CI
Age	≥75 years	33/2164 (1.5)	48/2187 (2.2)	1.45	0.93, 2.26)
	<75 years	18/3426 (0.5)	23/3434 (0.7)	1.28	(0.69, 2.38)
Prior MI or Stroke	Yes	6/291 (2.1)	10/280 (3.6)	1.73	(0.63, 4.75)
	No	45/5299 (0.8)	61/5341 (1.1)	1.35	(0.92, 1.99)
Hypertension	Yes	42/3146 (1.3)	58/3138 (1.8)	1.39	(0.94, 2.07)
	No	9/2444 (0.4)	13/2483 (0.5)	1.43	(0.61, 3.35)
Diabetes	Yes	15/748 (2.0)	14/697 (2.0)	1.03	(0.50, 2.13)
	No	36/4842 (0.7)	57/4924 (1.2)	1.56	(1.03, 2.37)
Hypercholesterolemia	Yes	24/2083 (1.2)	31/2088 (1.5)	1.28	(0.75, 2.19)
	No	27/3507 (0.8)	40/3533 (1.1)	1.49	(0.91, 2.43)
Smoking	Current/former	20/1628 (1.2)	25/1515 (1.7)	1.35	(0.75, 2.43)
	Never	31/3962 (0.8)	46/4105 (1.1)	1.44	(0.91, 2.27)
Afib/Aflutter	Yes	7/152 (4.6)	8/151 (5.3)	1.17	(0.42, 3.26)
	No	44/5438 (0.8)	63/5470 (1.2)	1.43	(0.98, 2.11)
Body Mass Index	≥25	30/2579 (1.2)	38/2569 (1.5)	1.28	(0.79, 2.07)
	<25	21/3002 (0.7)	33/3043 (1.1)	1.55	(0.90, 2.68)



Genetic, Clinical and Nonclinical Studies do not Support Biological Plausibility

Genetic

No evidence of premature cardiovascular disease in:

- Life-long absence of sclerostin (sclerotosis and Van Buchem disease)
- Non-coding *SOST* variants associated with a modest increase in bone mineral density[1]

Clinical

Phase 1, 2, and non-pivotal 3 did not identify a cardiovascular safety finding:

- Blood pressure
- Pulse
- ECG
- Labs
- Adverse events

No sclerostin expression in fibrous cap or endothelium

Nonclinical

No evidence of acute or chronic cardiovascular effects in:

- Monkeys
- Rats
- Mice, including:
  - sclerostin knockout
  - ovariectomized *ApoE* knockout

Cardiovascular Safety Conclusion

- **Discordant 12-month MACE results**
  - Study 337 no imbalance vs Study 142 with imbalance
  - Meta-analysis HR (95% CI) 1.39 (0.97, 2.00)
- **Given uncertainty, other considerations**
  - Study 142 alendronate arm behavior
  - 12-month other atherothrombotic events attenuate Study 142 imbalance
  - Estimated risk in overall study period
  - No subgroup with higher relative risk, including prior myocardial infarction or stroke
  - Lack of biological plausibility based on human genetic, nonclinical and clinical data

Benefit/Risk Assessment

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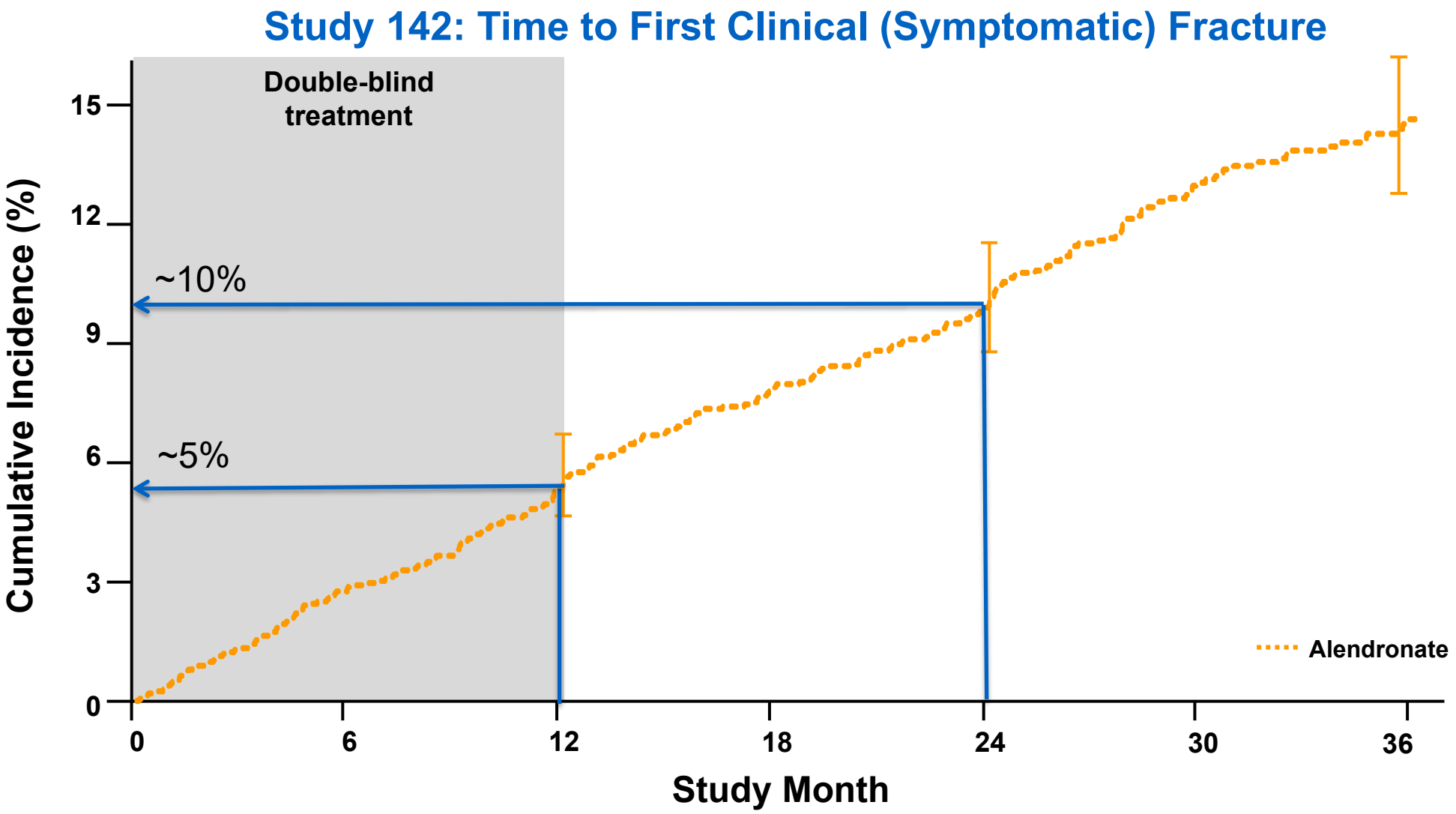
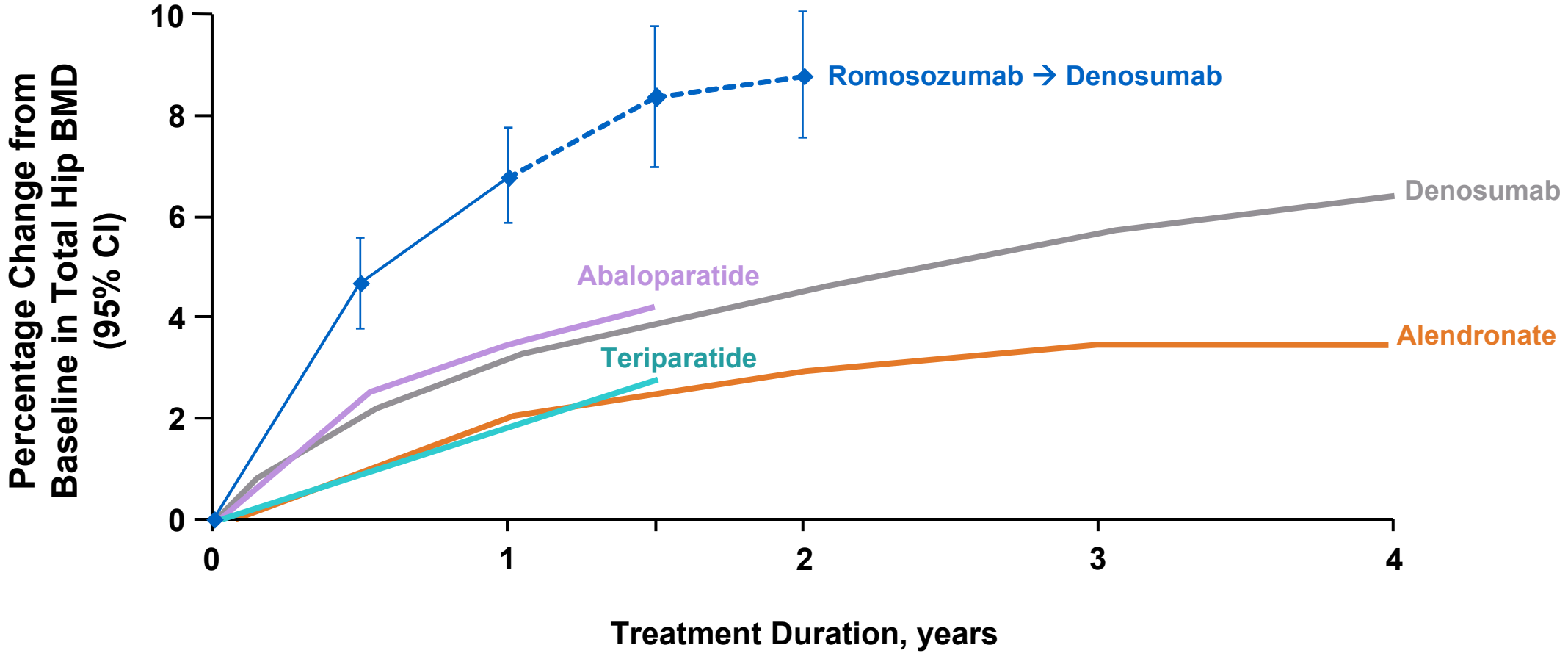
Women with Postmenopausal Osteoporosis Continue to Fracture Despite Current Therapy



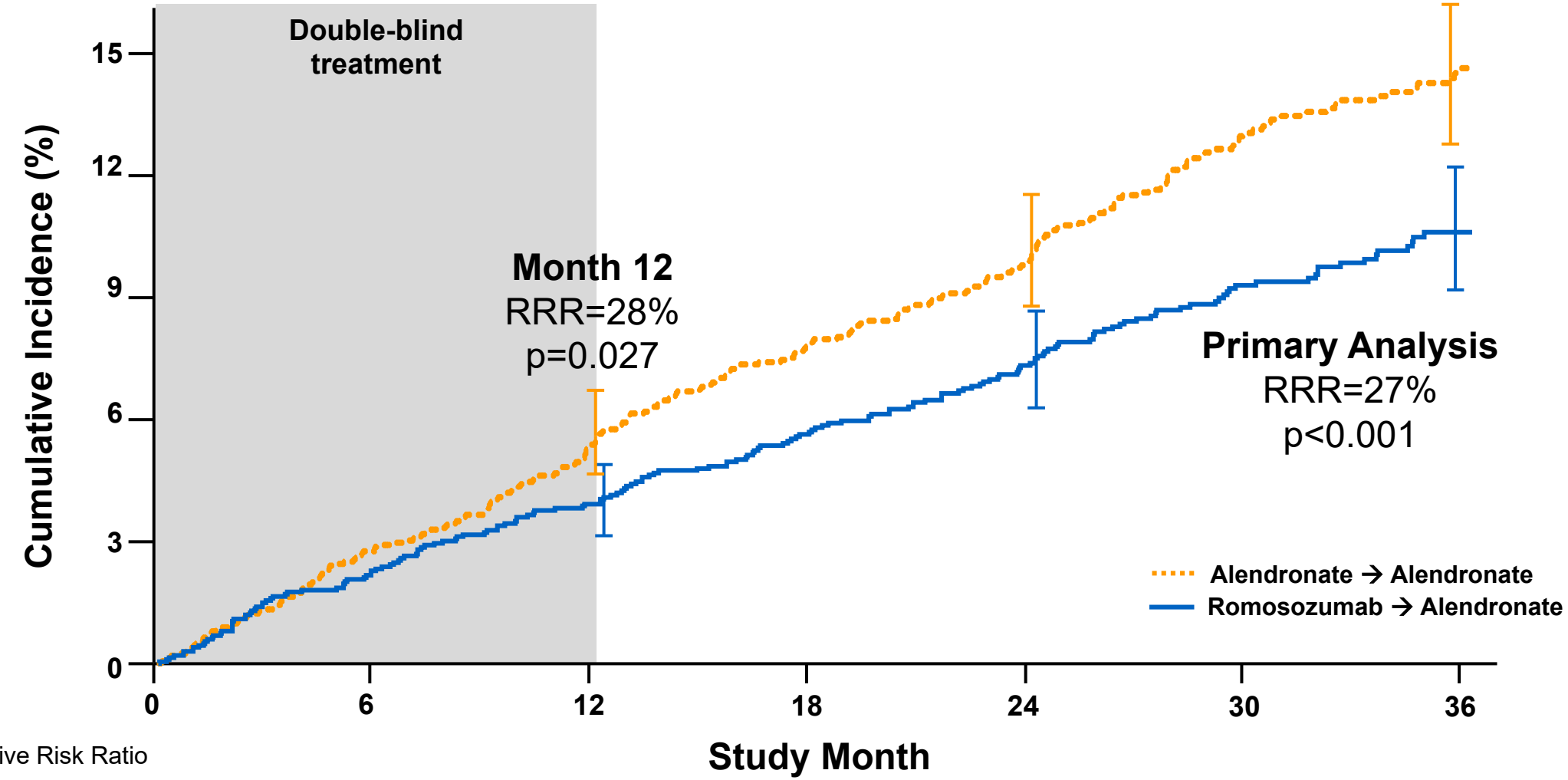
Total Hip Bone Mineral Density Changes in Postmenopausal Osteoporosis Studies



Adapted from Reid IR. *Nat Rev Endocrinol.* 2015;11:418-428. These cross-study data are provided for illustrative purposes only.

Robust, Early and Sustained Anti-fracture Efficacy

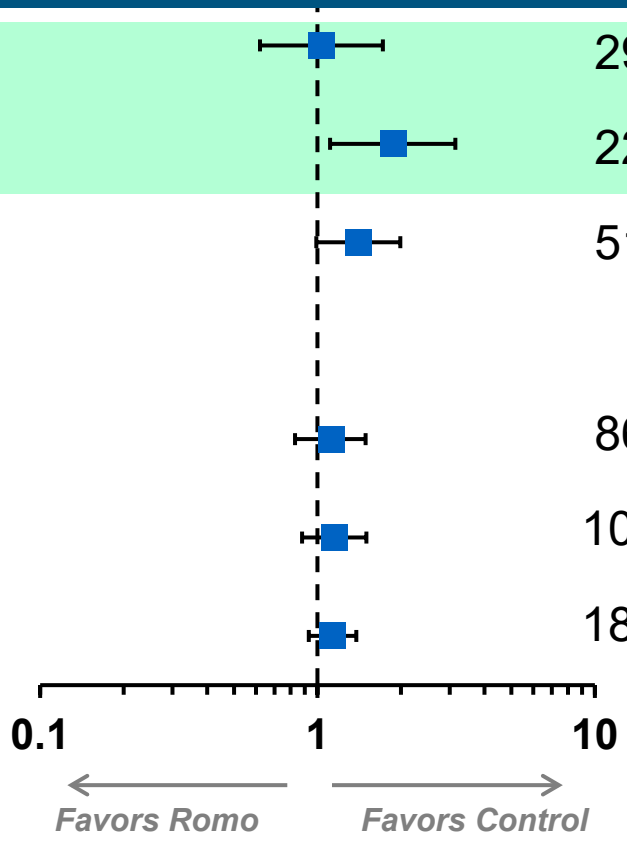
Study 142: Time to First Clinical (Symptomatic) Fracture



RRR=Relative Risk Ratio

Time to MACE in 12-month and Overall Study Period

	Study	Control N=5590 n (%)	Romo N=5621 n (%)	HR	95% CI
12-month Period	337	29 (0.8)	30 (0.8)	1.03	(0.62, 1.72)
	142	22 (1.1)	41 (2.0)	1.87	(1.11, 3.14)
	Meta	51 (0.9)	71 (1.3)	1.39	(0.97, 2.00)
Overall Study Period	337	86 (2.4)	95 (2.7)	1.12	(0.83, 1.49)
	142	102 (5.1)	117 (5.7)	1.15	(0.88, 1.50)
	Meta	188 (3.4)	212 (3.8)	1.13	(0.93, 1.38)



Time to MACE in 12-month and Overall Study Period

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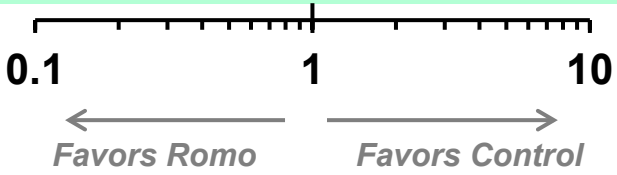
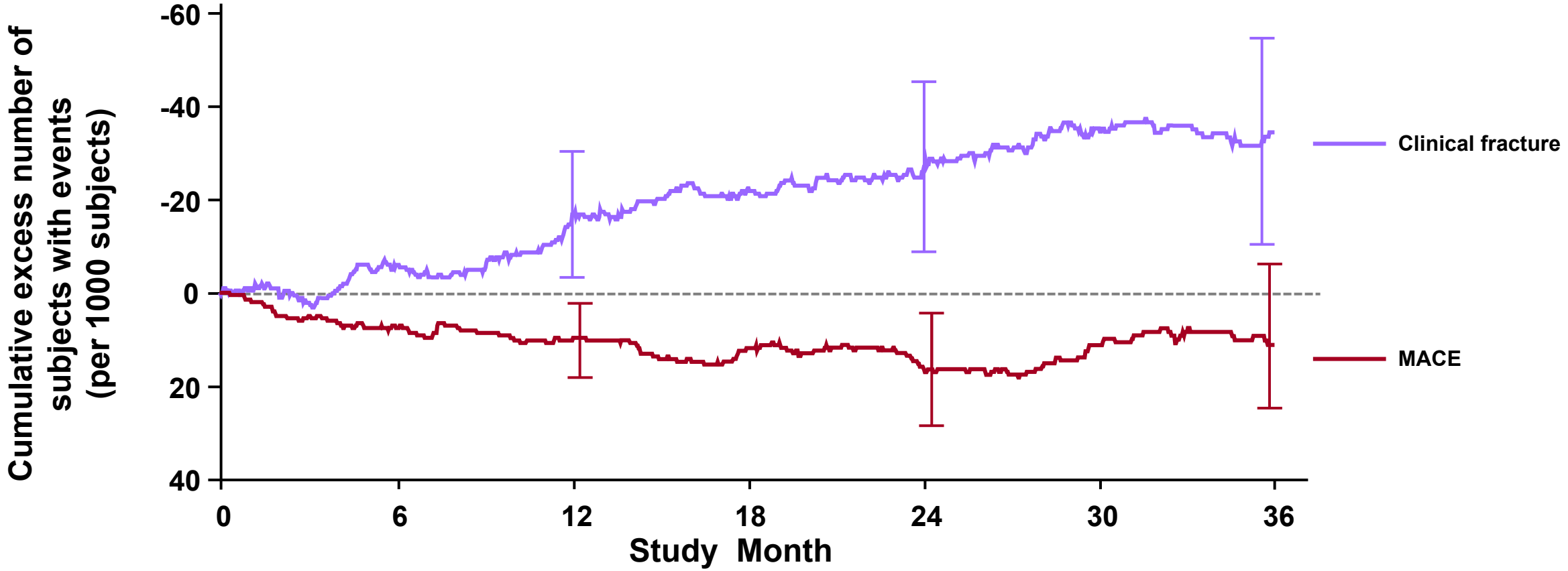


Quantitative Benefit/Risk Analysis Assumptions

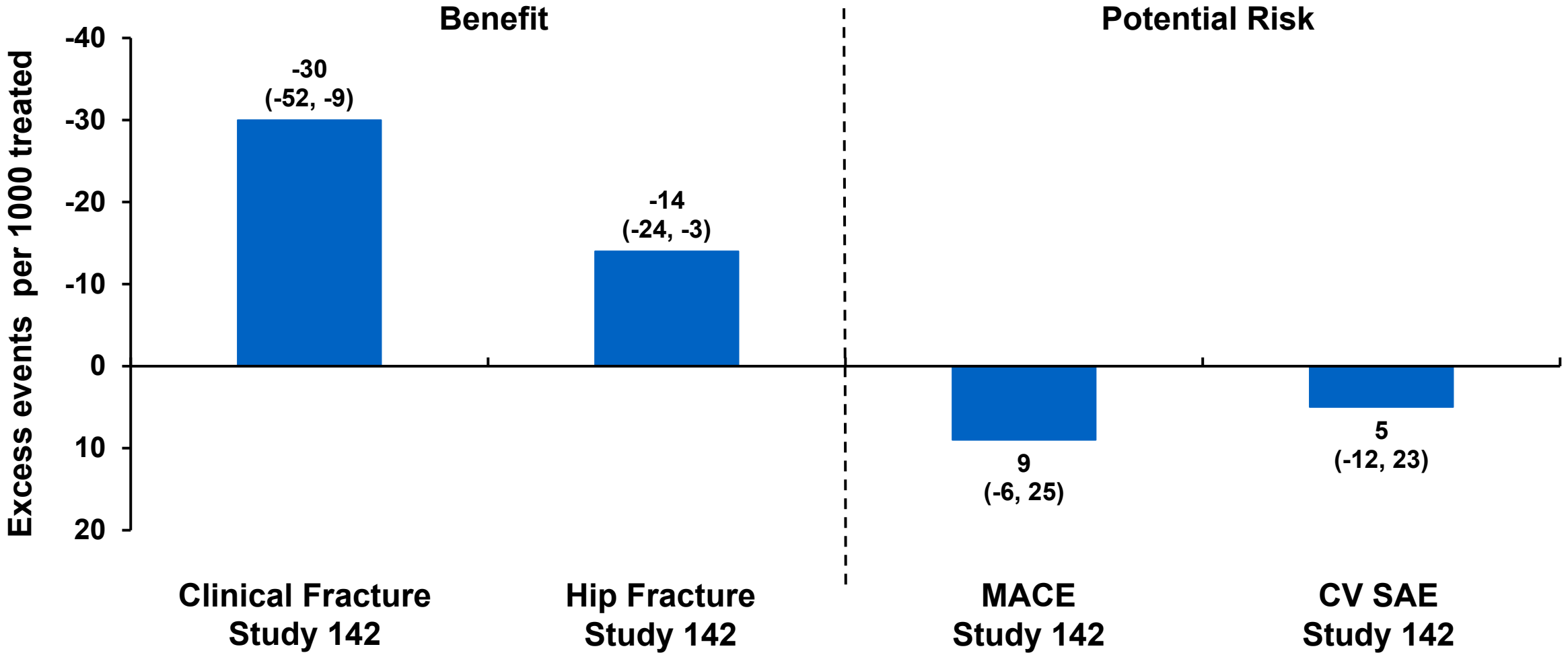
Variables	Assumptions
Principles	▪ Based on clinical trial data ▪ Analytic method using all data ▪ Holistic time-course
Dataset	Study 142 ▪ Primary endpoints of new vertebral fractures and clinical fractures ▪ Romosozumab-to-alendronate vs alendronate Supplemental: Meta-analysis
Time	3 years
Quantification	Kaplan-Meier incidence at 3 years
Benefits	▪ Clinical (symptomatic) fractures ▪ Hip fractures
Risks	▪ MACE ▪ CV SAE

Study 142: Temporal Benefit/Risk of Composite Clinical Fractures vs MACE

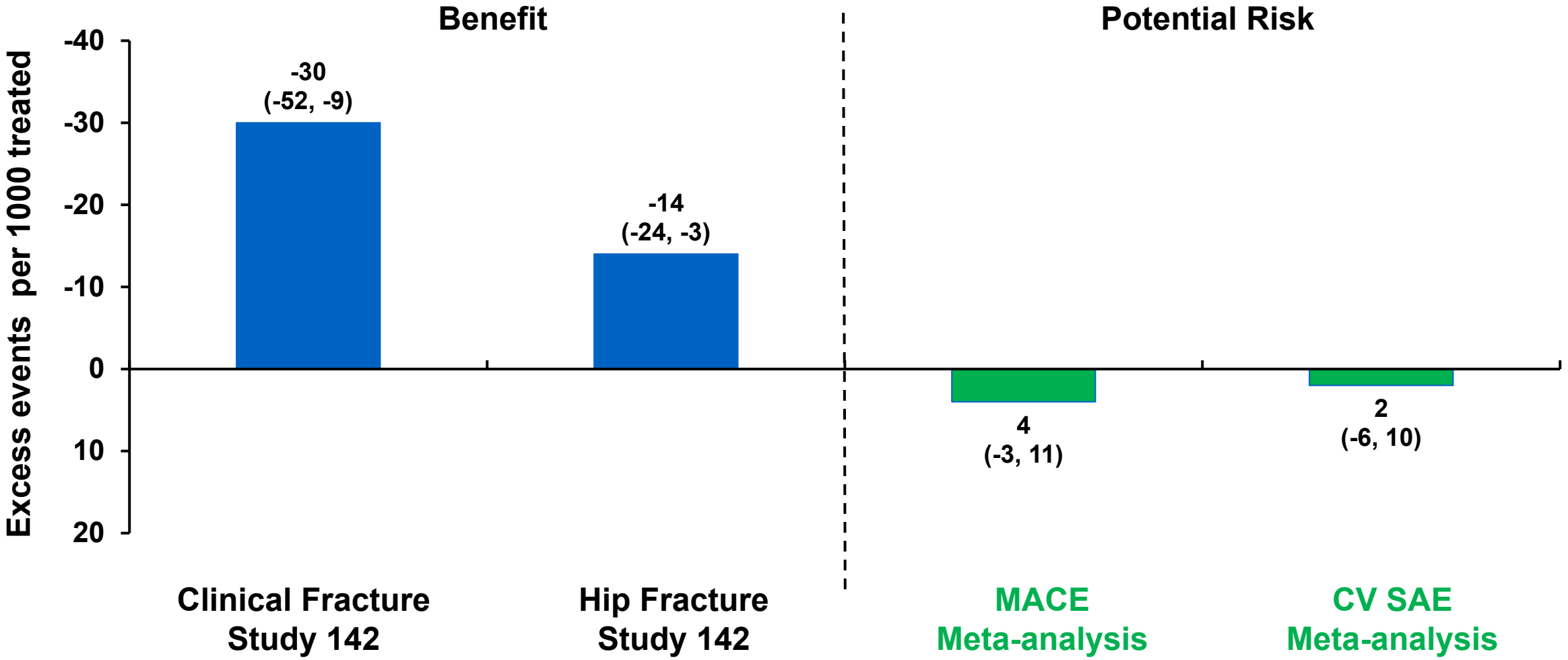
CR8



Study 142: Excess Number of Events (95% CI) per 1000 Patients Treated for 3 Years

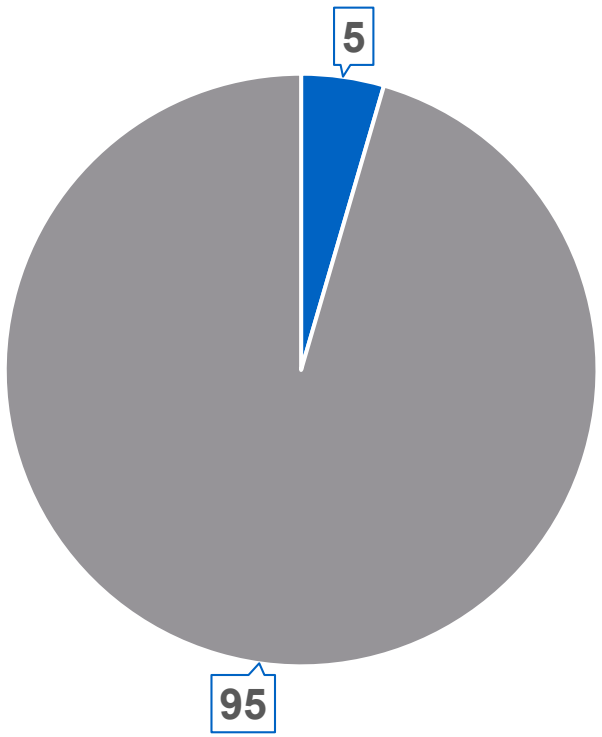


Study 142 and Meta-analysis: Excess Numbers of Events (95% CI) per 1000 Patients Treated for 3 Years

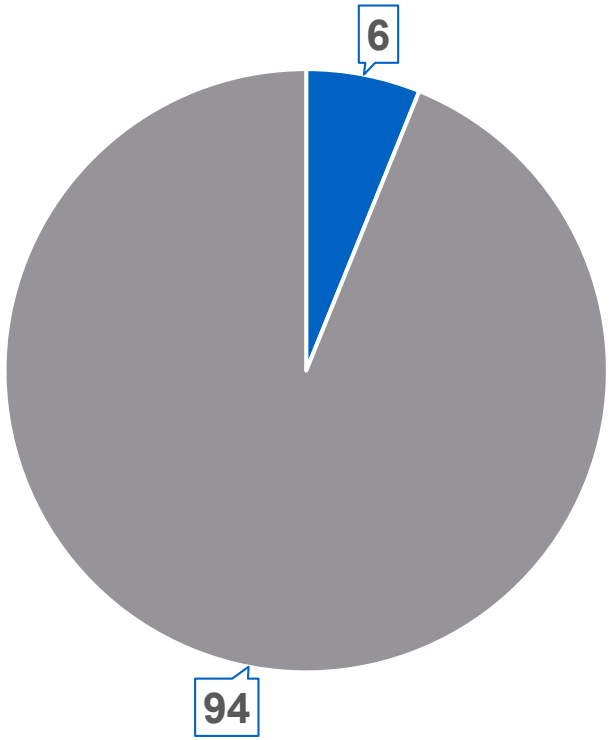


Studies 337/142 and Medicare: Population (%) With and Without a Prior Myocardial Infarction or Stroke

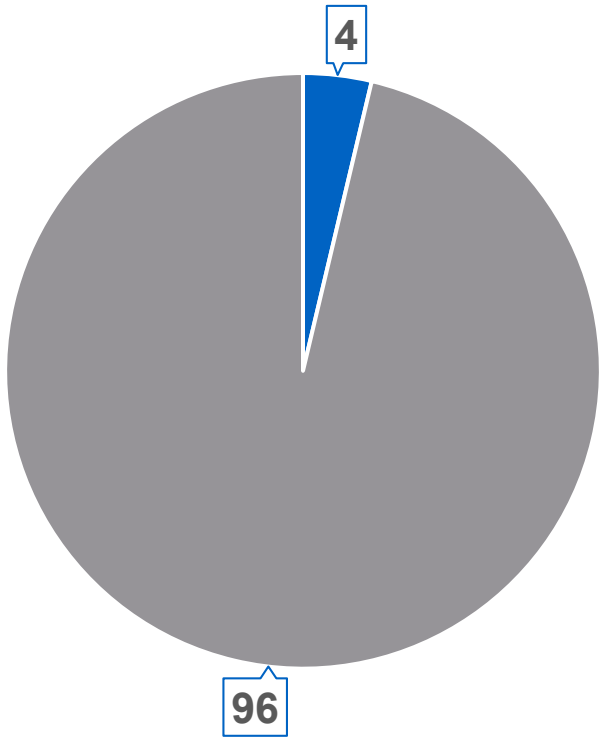
Study 337
N=7,157



Study 142
N=4,054

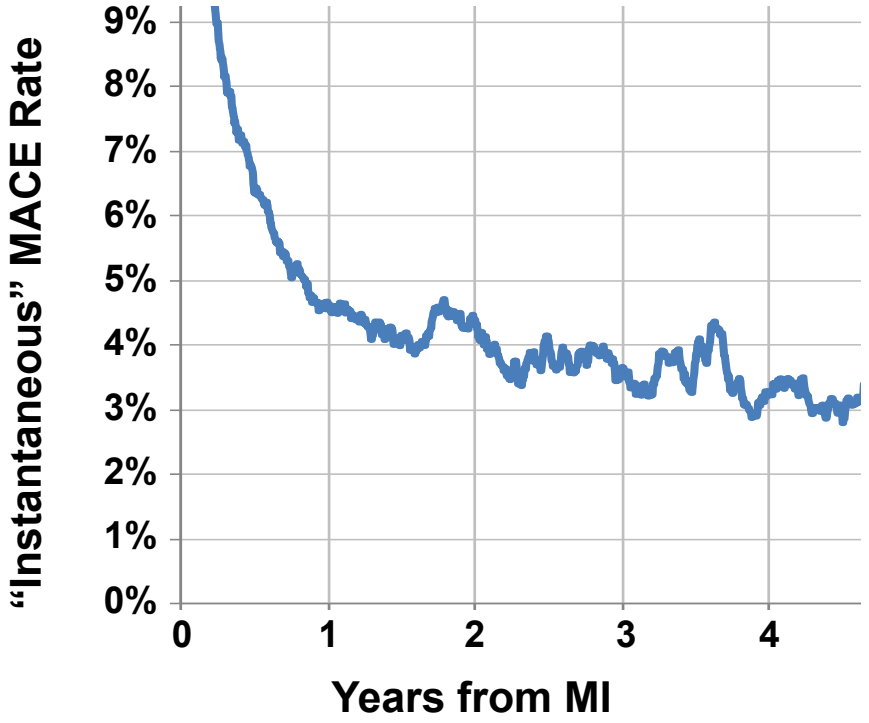


Medicare
N=1,442,551

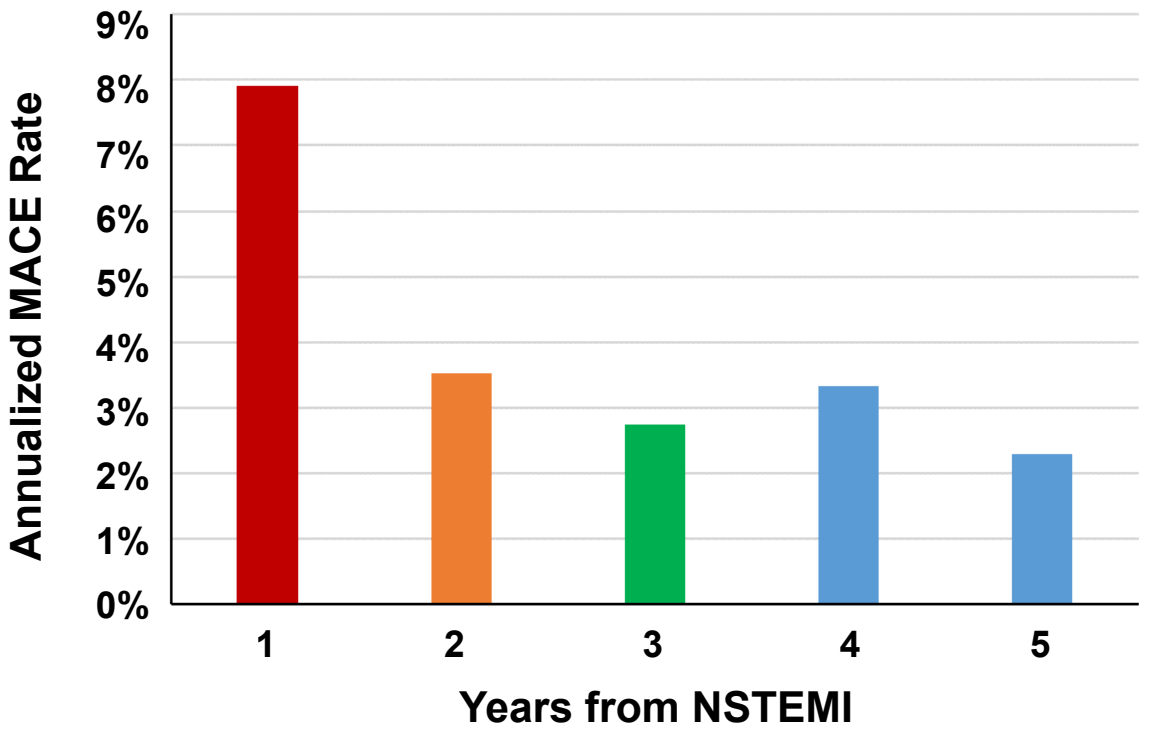


Highest Risk of MACE Immediately After Myocardial Infarction or Stroke

OPTUM Database: "Instantaneous" Rate of MACE After Myocardial Infarction



IMPROVE-IT: Landmark Analysis of Annual Rates of MACE in 4253 NSTEMI Patients on Simvastatin Alone Based on Years Since Event



Pharmacovigilance and Risk Management Plan

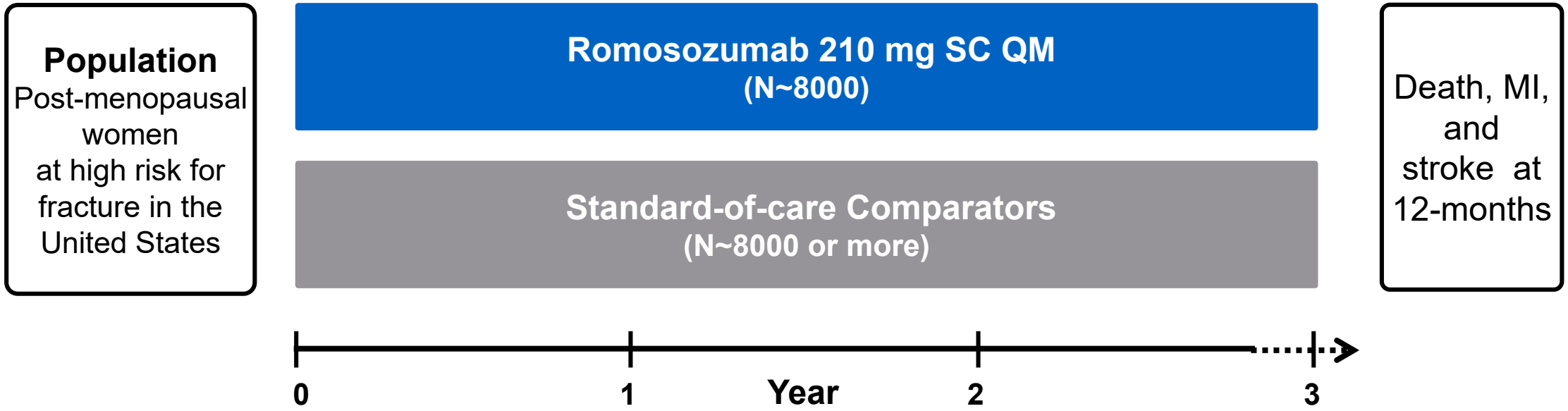
Safety Surveillance	Post-marketing Surveillance	▪ Routine signal detection/evaluation:
		  • Individual case safety report reviews
		  • Periodic Trend analyses
		  • Literature searches
		  • External databases (Vigibase, Eudravigilance and FDA Adverse Event Reporting System)
		▪ Detailed questionnaires for post-marketing myocardial infarction and stroke adverse event monitoring and evaluation

Education and Communication	Risk Communication	▪ Proposed labeling includes **boxed warning for myocardial infarction and stroke** ▪ Patient medication guide describes safety risks
	Education for HCPs and Patients	Additional available programs: ▪ Healthcare professional and patient education material ▪ Support call center
Additional Post-marketing Safety Surveillance	Post-marketing Pharmacovigilance Study	▪ Real-world observational study

Post-marketing Real-world Observational Study to Ensure Cardiovascular Risk is Not Underestimated

Consideration	Conclusion	Rationale
Pre-approval **vs** **Post-approval**	Post-approval	▪ Benefit/risk favorable in Study 142
Randomized controlled trial **vs** **Prospective observational study**	Prospective observational study	▪ Demonstrate relative risk of CV events does not exceed that observed in Study 142 (e.g., hazard ratio ~2) ▪ Real-world comparative safety study addresses need with: • appropriate precision • timeliness • appropriate population

Proposed Real-world Observational Comparative Safety Study Design



Hypothesis

Risk of death, MI, and stroke in US women with post-menopausal osteoporosis at high risk for fracture treated with romosozumab is less than Study 142 estimate (hazard ratio ~2)

Key Outcomes

- Description of US women exposed to romosozumab and matched cohort
- Incidence of death, MI, and stroke during 12-month treatment period

Real-world Observational Study Design Elements to Address Challenges

Challenges	Mitigation
Population of interest	Data sources capture large proportion of eligible US women: • Medicare (>90% US population ≥65 years) • United Healthcare: commercial and Medicare Advantage plans • Truven Marketscan: commercial and Medicare Supplemental plans
Patient exposure	• Codes identify patients receiving prescriptions • Medical chart-validated algorithms to identify patients receiving treatment
Sample Size	• ~1.4M US women with PMO at high risk of fracture • Anticipate ~8,000 women on romosozumab in Medicare within 2 years
Safety outcomes	• Death, myocardial infarction, stroke – validated algorithms with high positive predictive value against medical charts
Covariates and confounders	• Captures demographics, concomitant medications, comorbidities, health resource utilization • Limitation: plausible covariates not in claims include severity of underlying bone disease • Analytic methods to mitigate and assess impact of measured and unmeasured confounders

Presentation Overview

Introduction	**Scott Wasserman, MD** Vice President, Global Development, Amgen
Unmet Medical Need	**Michael McClung, MD** Founding Director, Oregon Osteoporosis Center
Clinical Efficacy	**Rachel Wagman, MD** Executive Medical Director, Global Development, Amgen
Safety and Benefit/Risk	**Scott Wasserman, MD** Vice President, Global Development, Amgen
Amgen Conclusion	**Steven Galson, MD, MPH** Senior Vice President, Global Regulatory Affairs and Safety, Amgen
Clinician Perspective	**Felicia Cosman, MD** Professor of Medicine, Columbia University

Conclusion

Steven Galson, MD, MPH

Senior Vice President, Global Regulatory Affairs and Safety
Amgen Inc.

Benefit-Risk Summary

- Serious fractures may be as consequential as MI or stroke
- Superior fracture reduction with romosozumab weighed against *possible* increased CV risk
- Favorable benefit/risk can be achieved in clinic
- Labeling to warn of possible risk of MI and stroke

Amgen Post-marketing Commitments

- **Pharmacovigilance to monitor safety**
- **High quality observational study**
  - Confirm CV risk not greater than seen in Study 142
  - Provide additional safety information from U.S. clinical practice

Responsible Labeling and Communication

- **A boxed warning is proposed to communicate the potential risk of MI and stroke**
- **FDA Labeling Guidance**
  - A boxed warning is to be used when it is essential to consider the risk in appropriate patient selection and treatment decisions

Romosozumab is an Important Treatment Option

Proposed for women with postmenopausal osteoporosis at high risk for fracture

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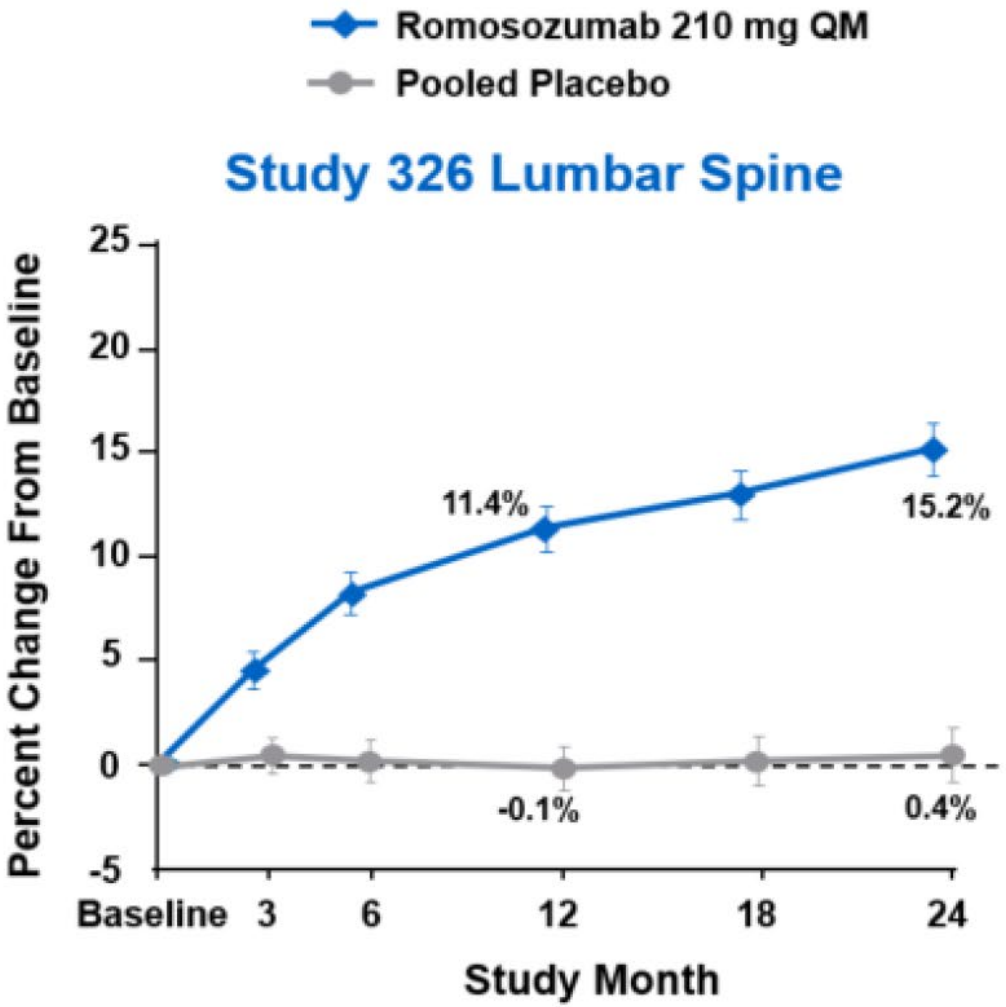
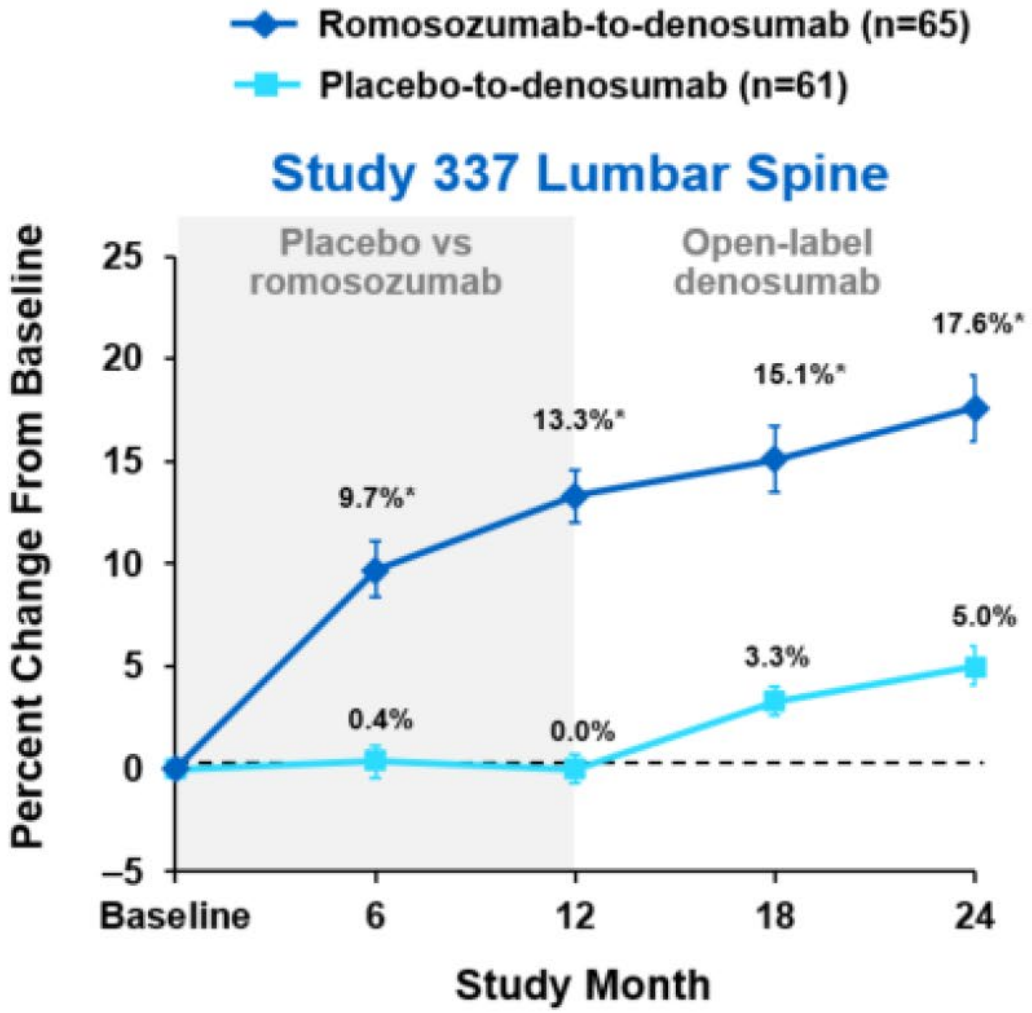
BACKUP SLIDES SHOWN

F9 pg 27. Comparison of Lumber Spine BMD Increases Over 24 Months in Study 326 and in Study 337



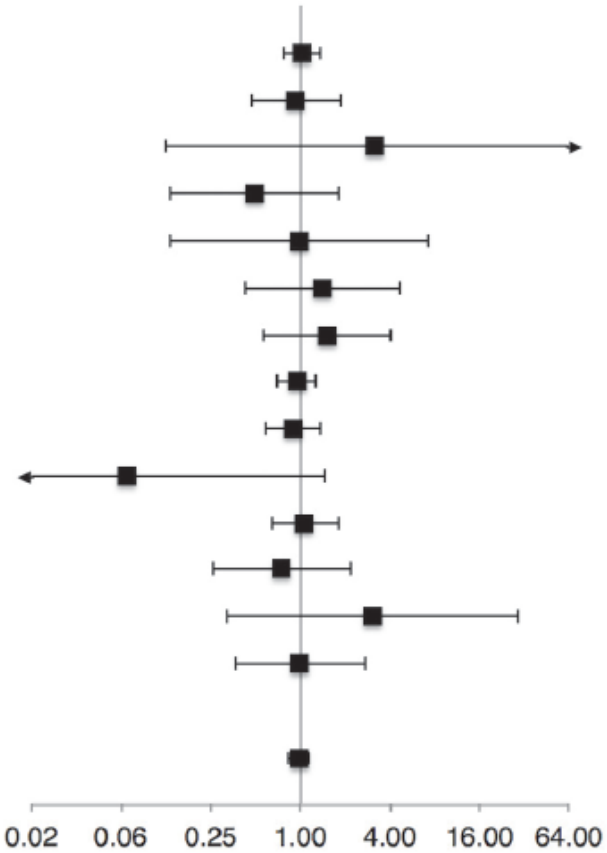


Source: CSRs 326 and 337

Meta-Analysis of Total Adverse Cardiovascular Events Associated with Use of Bisphosphonates

Outcome:		Bisphosphonate		Control		M-H	
Total CV Events	Bisphosphate	N Total	N Events	N Total	N Events	Pooled OR	(95% CI)
EPIC (1998)	Alendronate	997	179	502	88	1.02	(0.78, 1.35)
Orwoll (2000)	Alendronate	146	23	95	16	0.94	(0.47, 1.86)
Chevrel (2006)	Alendronate	31	1	33	0	3.19	(0.13, 81.3)
Lems (2006)	Alendronate	94	4	69	6	0.49	(0.13, 1.80)
McClung (2006)	Alendronate	47	2	46	2	0.98	(0.13, 7.24)
Eastell (2011)	Alendronate	57	7	57	5	1.40	(0.42, 4.67)
Adami (2004)	Ibandronate	392	23	128	5	1.50	(0.56, 4.03)
IVF (2004)	Ibandronate	1911	129	949	68	0.94	(0.70, 1.28)
VERT-MN (2000)	Risedronate	815	68	407	38	0.89	(0.59, 1.35)
Shiraki (2003)	Risedronate	125	0	43	2	0.07	(0.00, 1.47)
Boonen (2012)	Zoledronic acid	588	31	611	30	1.07	(0.64, 1.80)
Bai (2013)	Zoledronic acid	242	6	241	8	0.75	(0.26, 2.19)
Chao (2013)	Zoledronic acid	327	3	333	1	3.06	(0.32, 29.5)
Dalbeth (2014)	Zoledronic acid	50	9	50	9	1.00	(0.37, 2.73)
Combined		**5822**	**485**	**3564**	**278**	**0.98**	**(0.84, 1.14)**

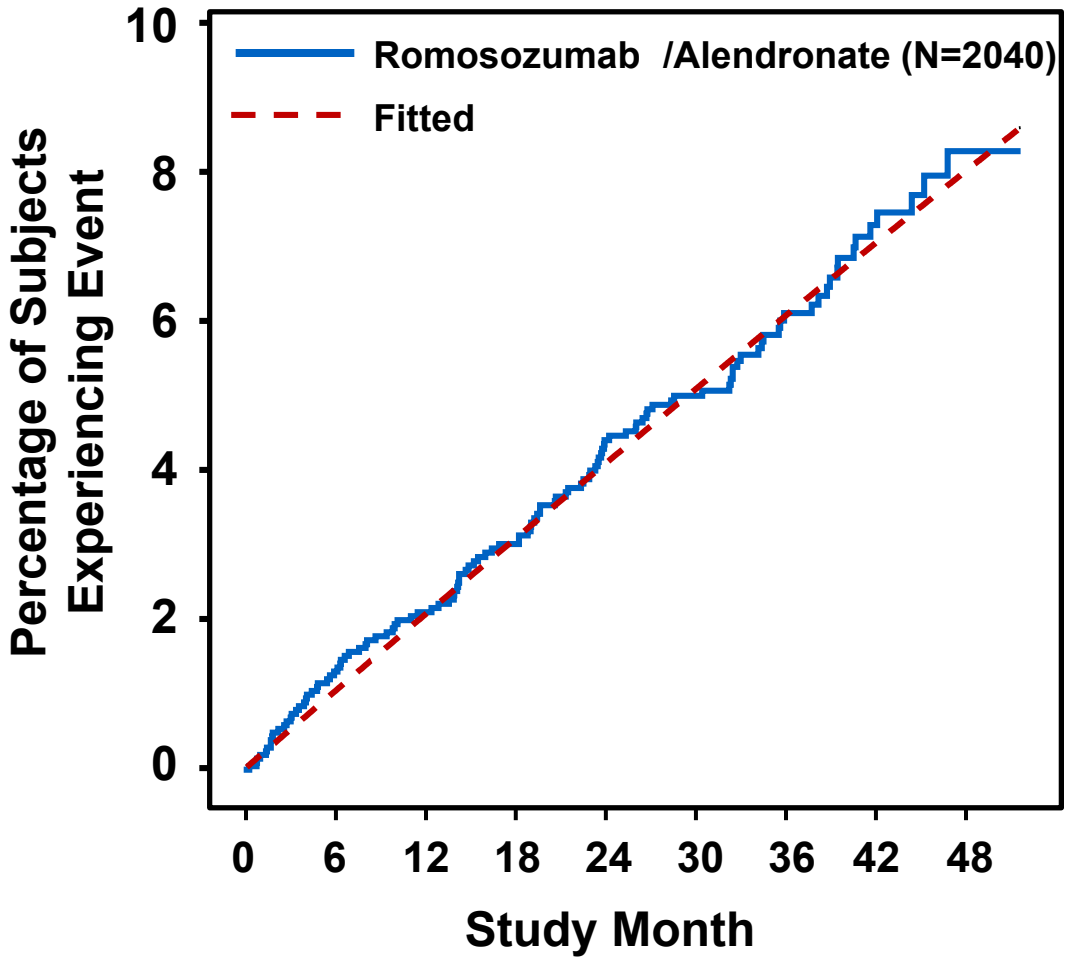
Cochran's Q = 7.25, p = 0.89, I^2 = 0.0%

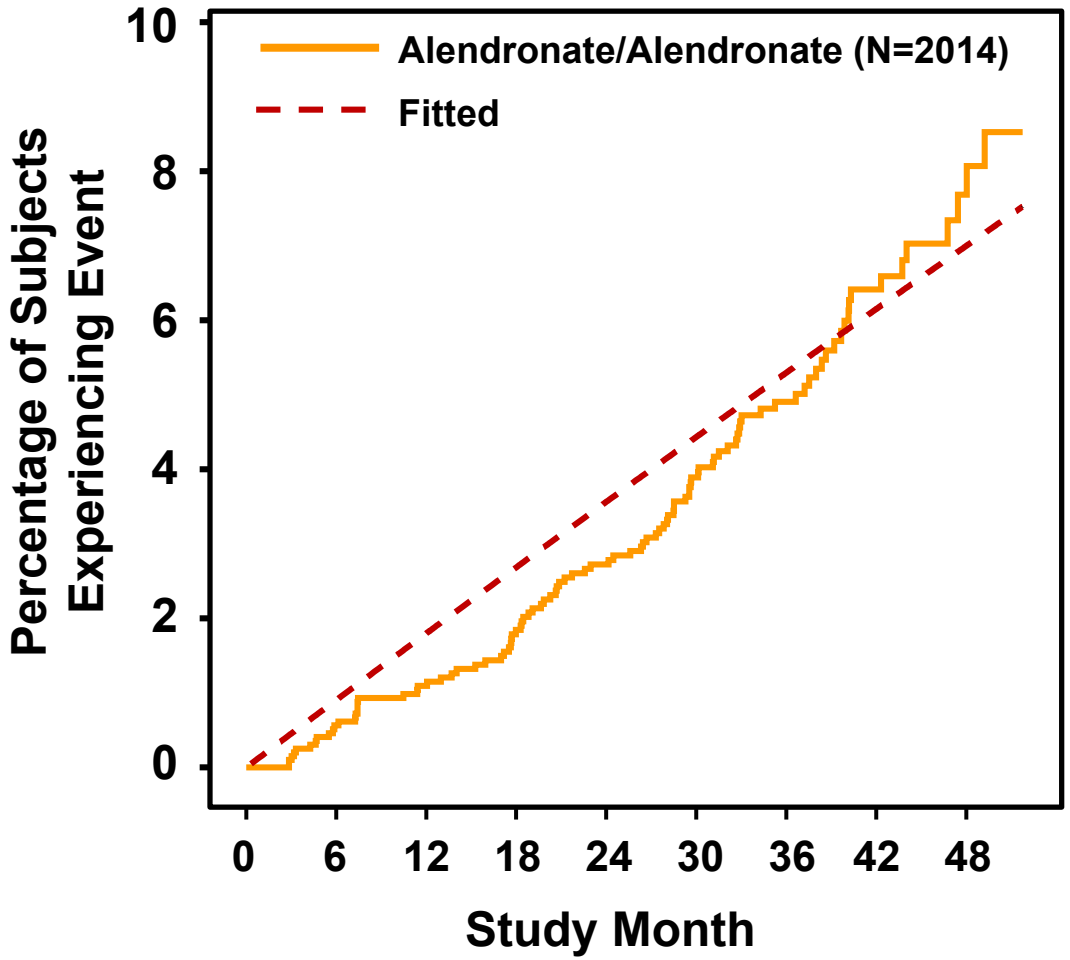


Abbreviations: CI, confidence interval; CV, cardiovascular; EPIC, Early Postmenopausal Intervention Cohort study; IVF, IntraVenous Fracture study; M-H, Mantel Haenszel; OR, odds ratio; VERT-MN, Vertebral Efficacy with Risedronate Therapy Multinational Study.

Source: Kim DH, et al. (2015) Bisphosphonates and Risk of Cardiovascular Events: A Meta-Analysis. PLoS ONE 10(4): e0122646. doi:10.1371/journal. pone.0122646.

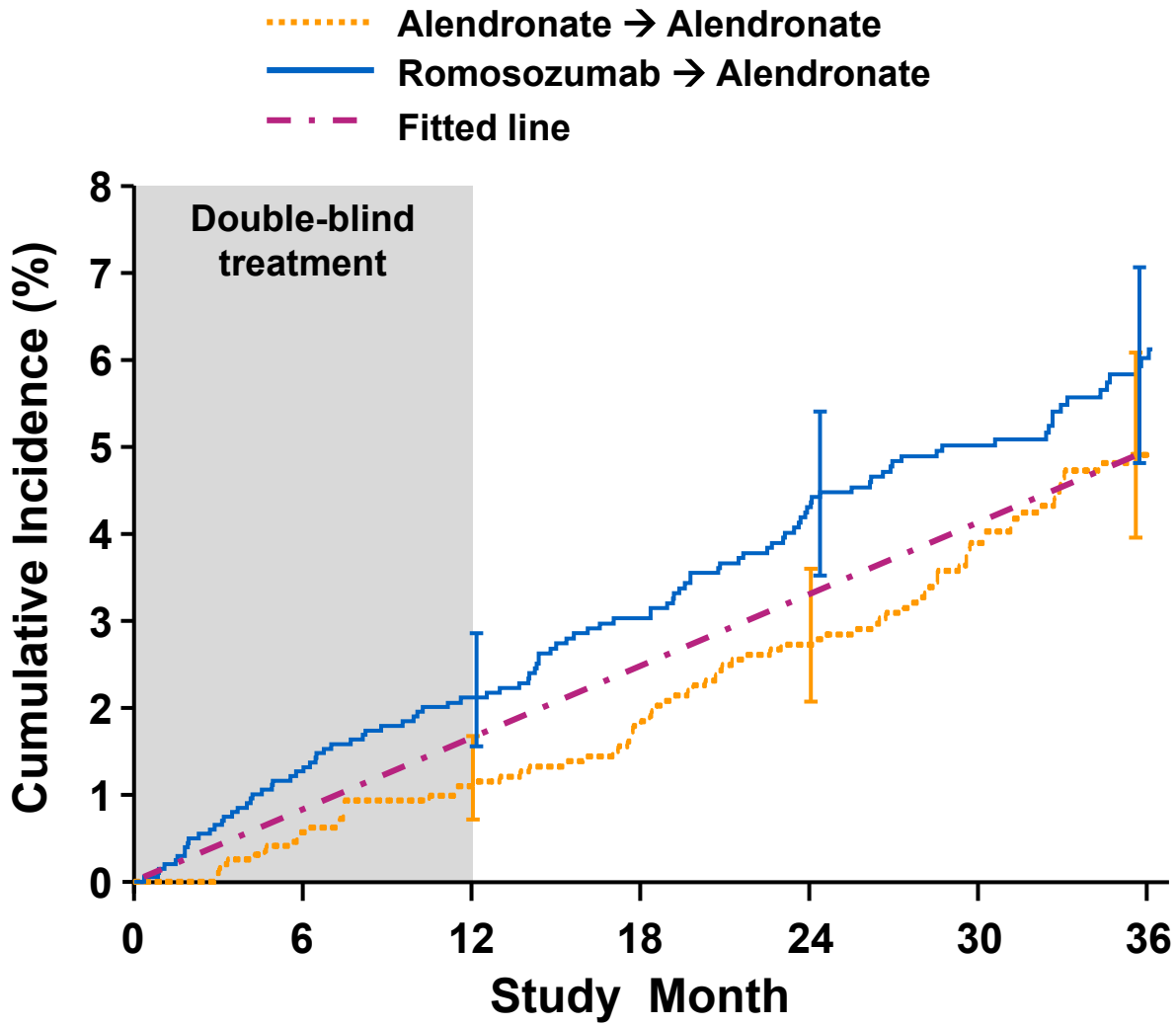
Study 142: Time to First MACE





N = Number of subjects who received at least 1 dose of active investigational product in the 12-month double-blind period. The timepoint for study month 36 is set at study day 1082 (study day 1096 - 14 days). Death events include fatal events adjudicated as cardiovascular-related or undetermined.

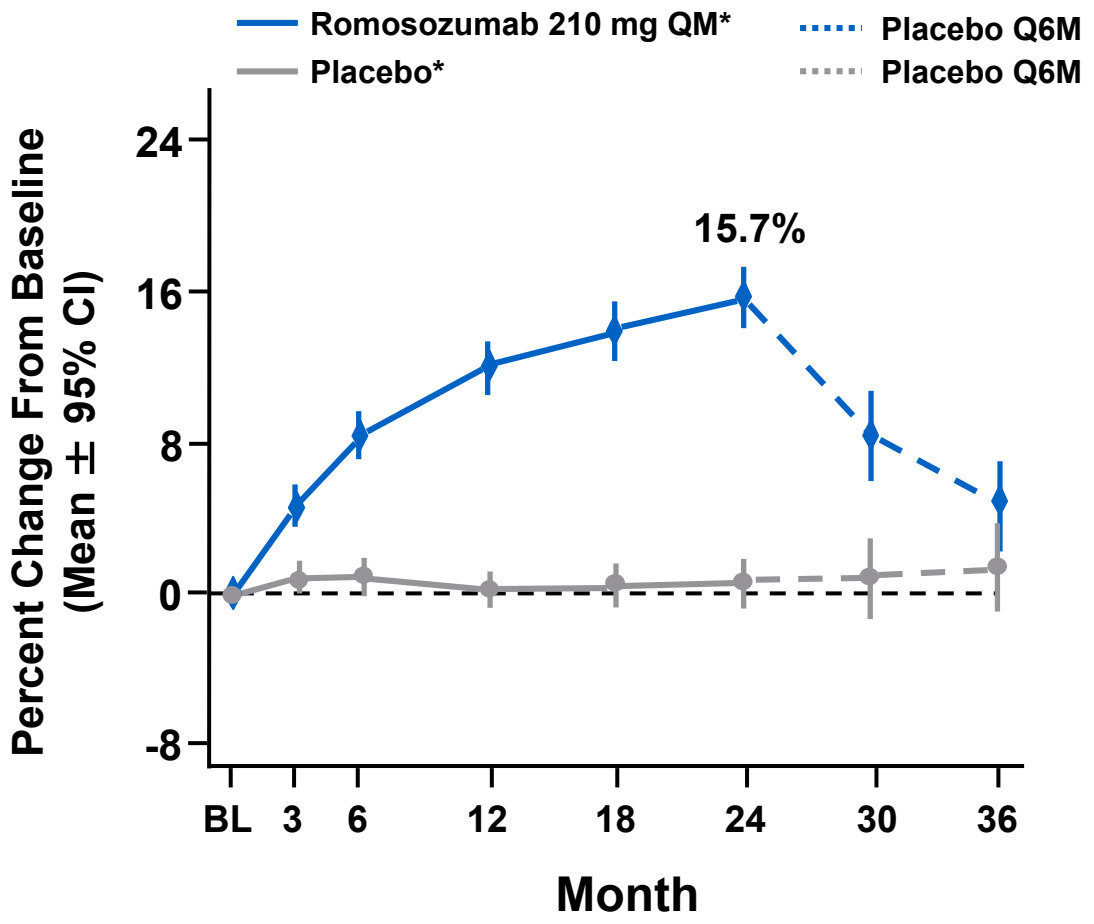
Study 142: Time to First MACE: Expected Hazard Ratio



	Alendronate n (%)	Romosozumab n (%)
Observed		
1 Years	22 (1.1)	41 (2.0)
3 Years	81 (4.9)	104 (5.8)
Expected based on linear event rate		
1 Year	27 (1.6)	41 (2.0)

Study	Expected HR based on linear event rate (IQR)
142	1.30 (1.15, 1.48)
337	1.06 (0.92, 1.20)
Meta (142, 337)	1.19 (1.08, 1.29)

Study 326: Lumbar Spine BMD Through Month 36

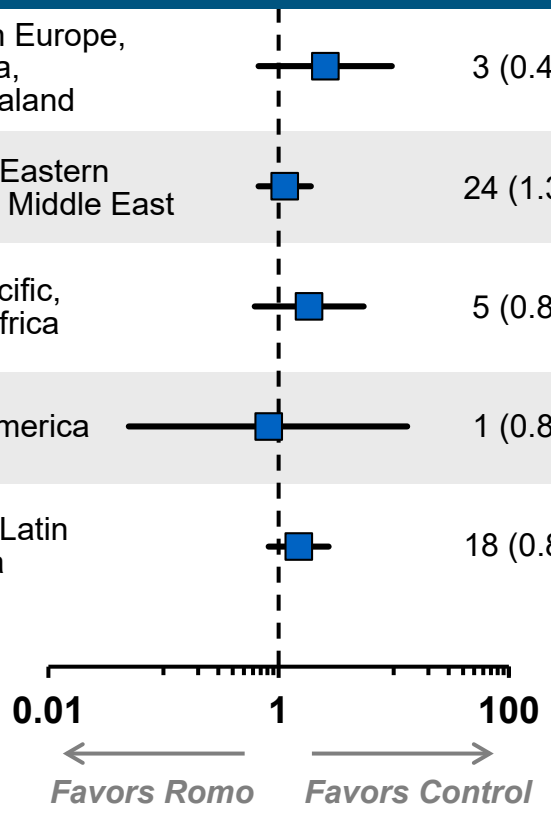


*Randomized treatment group up to month 24. Romosozumab 210 mg QM (n = 40), Placebo (n = 36).
Results include only subjects re-randomized to placebo at month 24.
McClung MR, et al. Presented at: ASBMR annual meeting. September 12-14, 2014. Houston, TX. Abstract 1152 and oral presentation.

Meta-analysis (337, 142): Time to First Positively Adjudicated MACE Event by Geographic Region

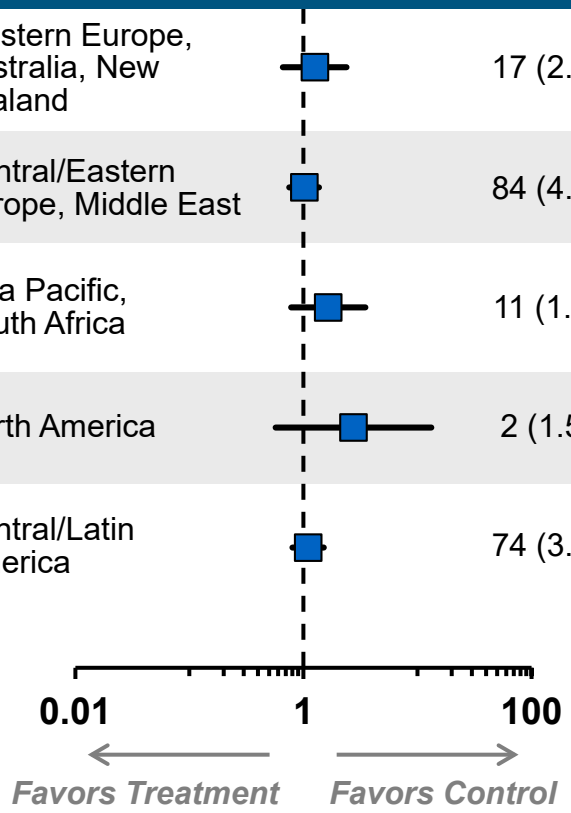
12-month Period

Region	Control N=5590 n (%)	Romo N=5621 n (%)	HR	95% CI
Western Europe, Australia, New Zealand	3 (0.4)	7 (0.9)	2.34	(0.60, 9.03)
Central/Eastern Europe, Middle East	24 (1.3)	29 (1.5)	1.18	(0.69, 2.03)
Asia Pacific, South Africa	5 (0.8)	9 (1.4)	1.84	(0.62, 5.48)
North America	1 (0.8)	1 (0.6)	0.82	(0.05, 13.11)
Central/Latin America	18 (0.8)	25 (1.1)	1.42	(0.78, 2.61)



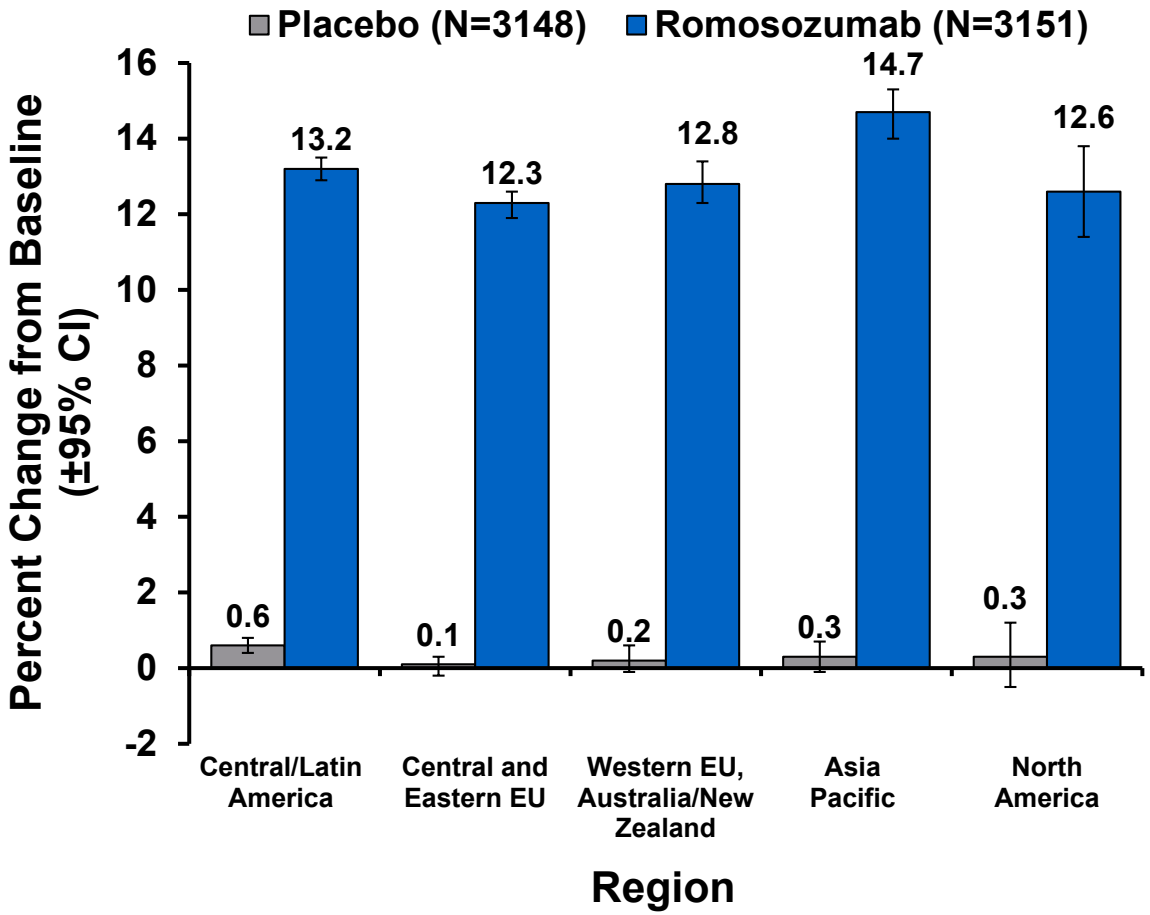
Overall Study Period

Region	Control N=5590 n (%)	Treatment N=5621 n (%)	HR	95% CI
Western Europe, Australia, New Zealand	17 (2.3)	21 (2.8)	1.26	(0.66, 2,39)
Central/Eastern Europe, Middle East	84 (4.6)	88 (4.7)	1.02	(0.75, 1.37)
Asia Pacific, South Africa	11 (1.7)	18 (2.9)	1.65	(0.78, 3.50)
North America	2 (1.5)	7 (4.4)	2.75	(0.57, 13.24)
Central/Latin America	74 (3.3)	78 (3.5)	1.10	(0.80, 1,51)



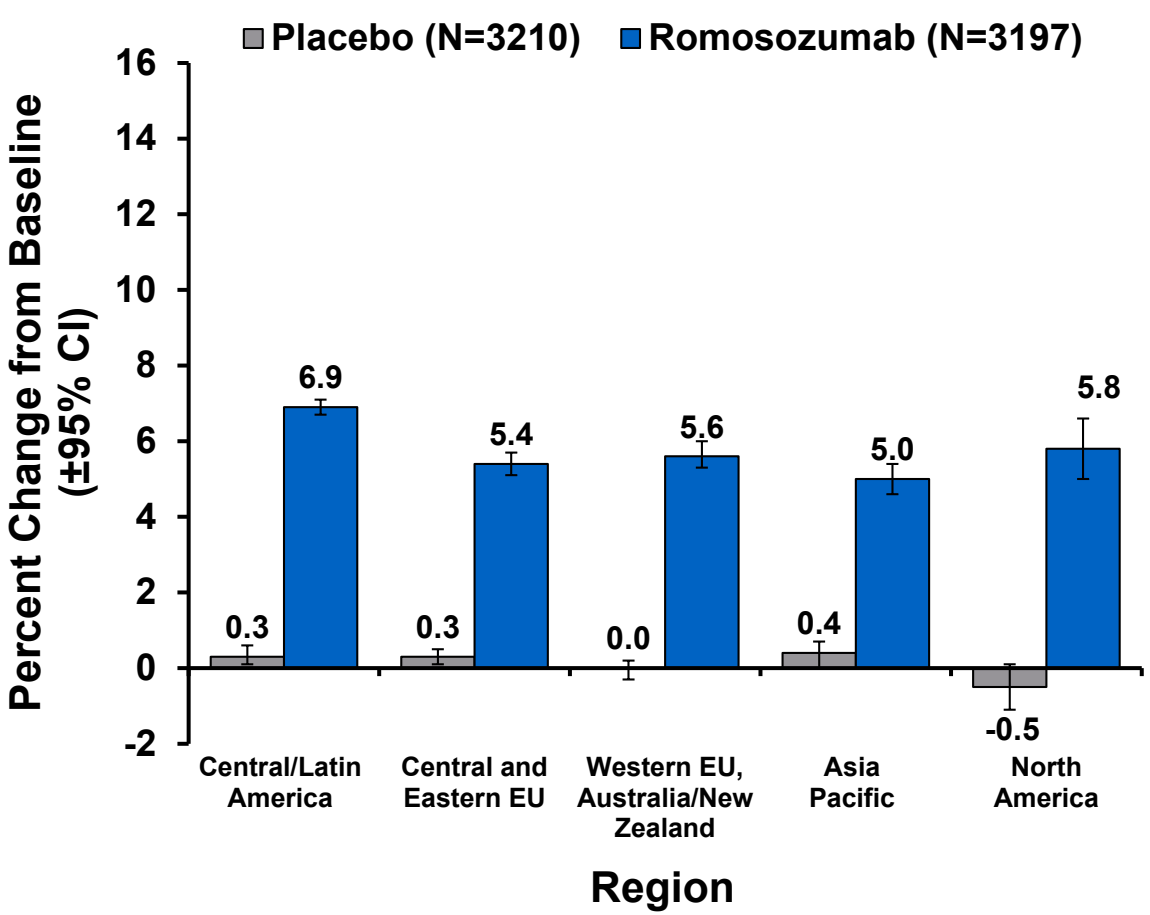
Study 337: BMD Responses at Month 12 at Lumbar Spine and Total Hip By Region

Lumbar Spine



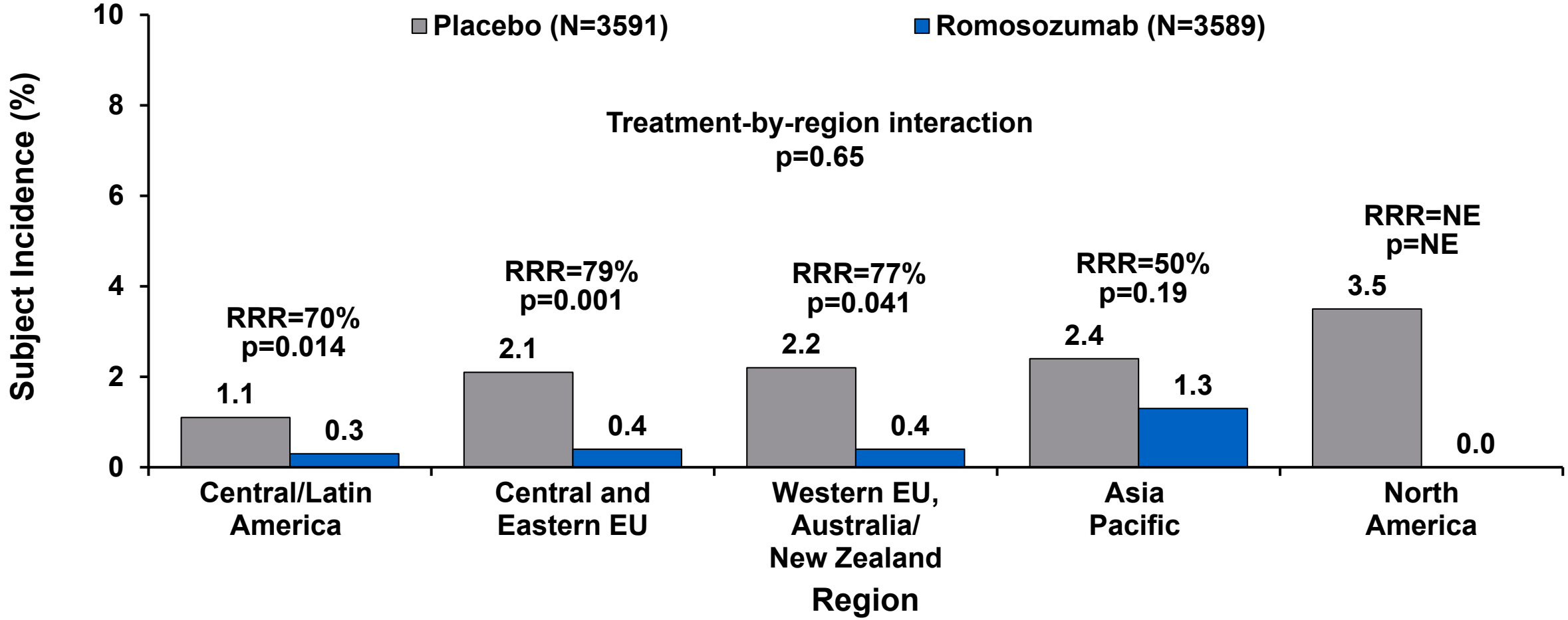
Placebo, n=	1368	865	445	391	79
Romo, n=	1395	873	430	364	89

Total Hip



Placebo, n=	1377	892	453	406	82
Romo, n=	1390	887	442	381	97

Study 337: New Vertebral Fracture Through Month 12 by Region



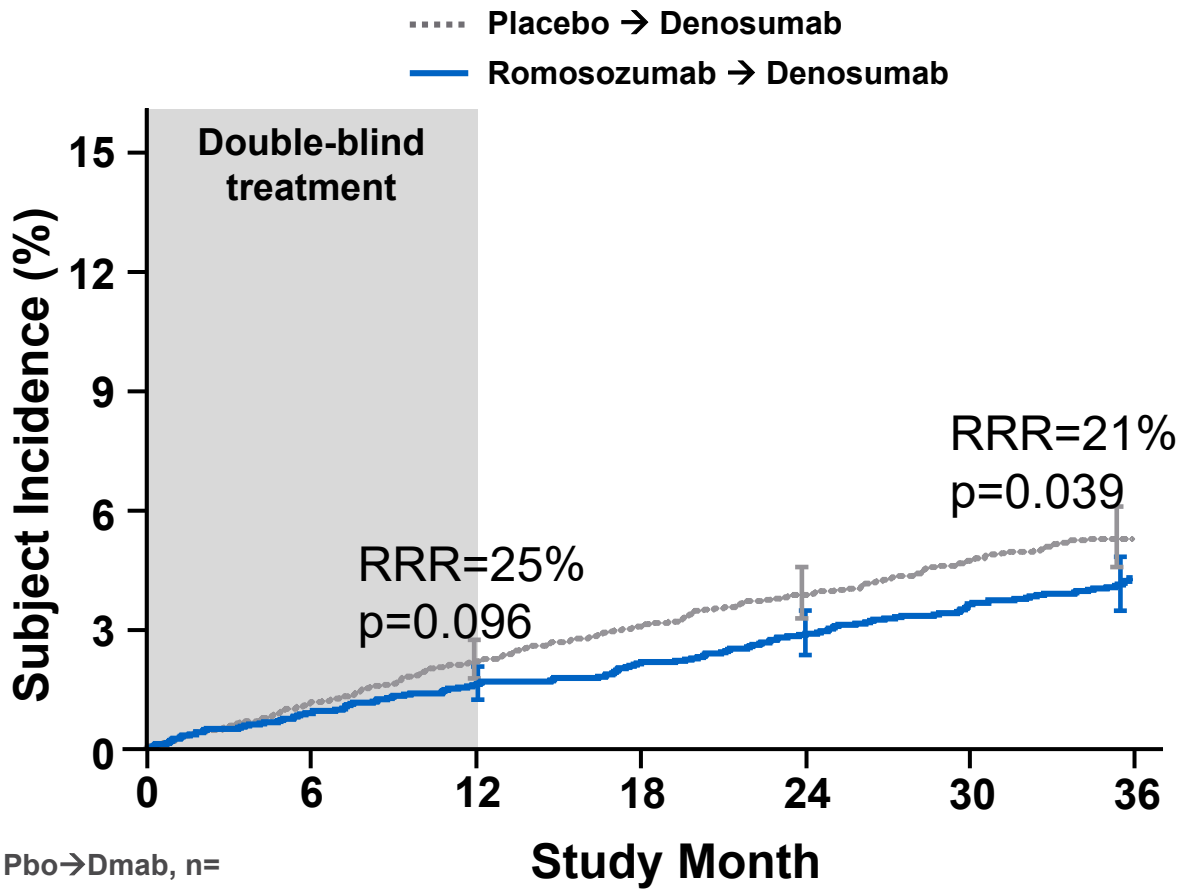
Placebo n/N1 =	16/431	20/929	10/466	10/411	3/86
Romosozumab n/N1 =	5/1494	4/915	2/453	5/392	0/97

n/N1 = number of fractures/number of subjects in the primary analysis set. NE = not estimable

Studies 337 and 142: Time to First Nonvertebral Fracture Through 36 Months

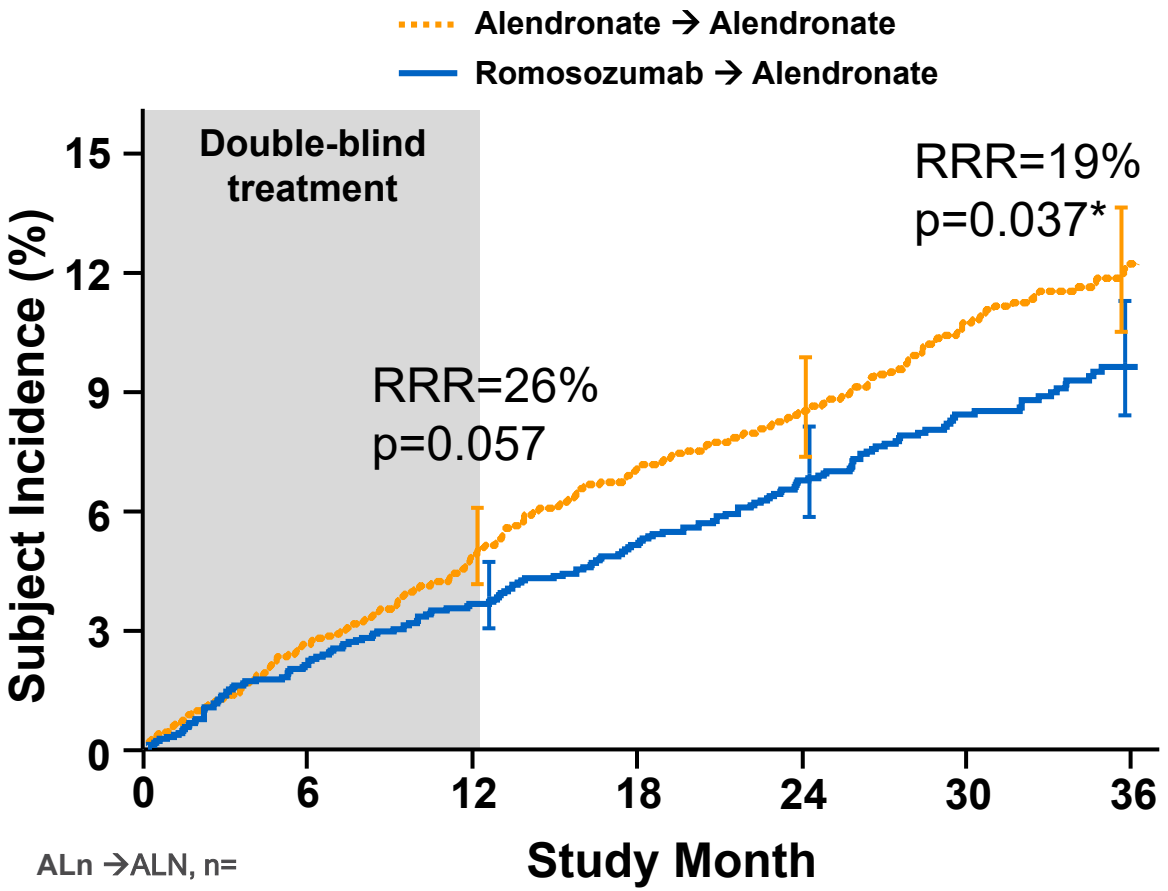
EF3057

Study 337



Pbo→Dmab, n=	3591	3317	3144	3050	2956	2850	2750
Romo→Dmab, n=	3589	3318	3149	3050	2959	2841	2738

Study 142

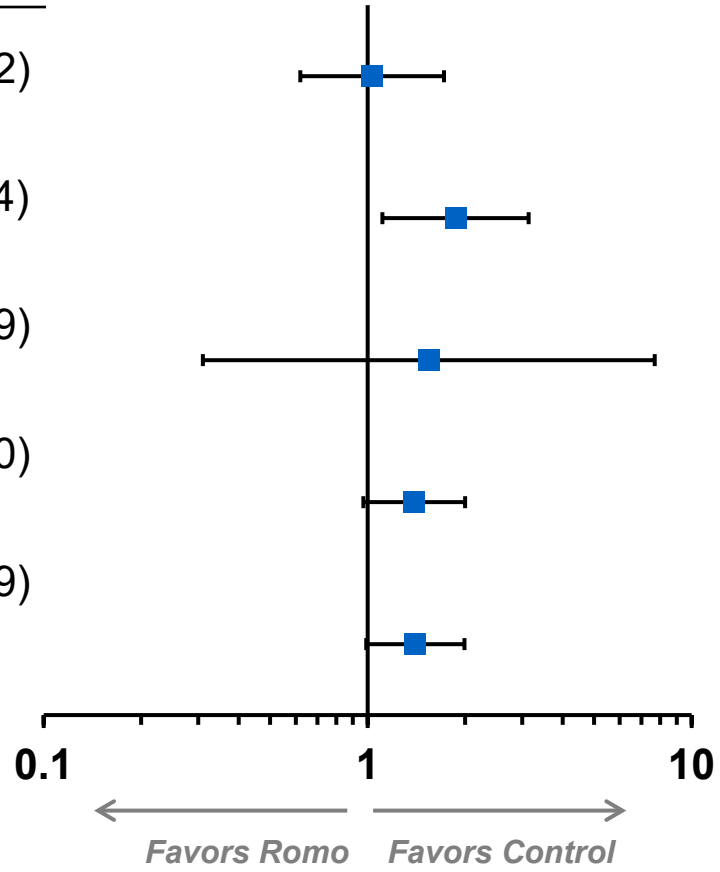


ALn →ALN, n=	2047	1873	1755	1661	1590	1097	730
Romo →ALN, n=	2046	1867	1776	1693	1627	1114	757

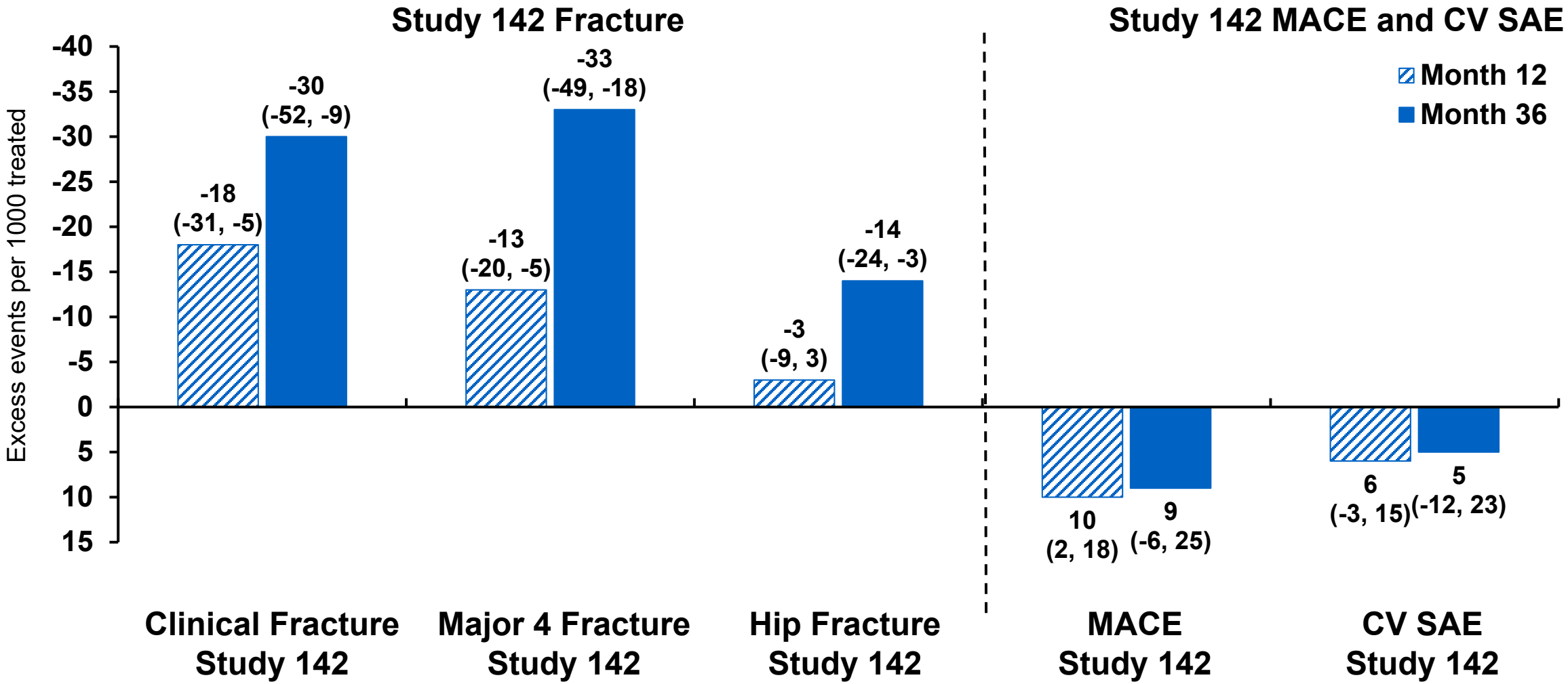
*multiplicity adjusted

Time to First MACE at Month 12

Study	Control n/N (%)	Romosozumab n/N (%)	Hazard Ratio (95% CI)
337	29/3576 (0.8)	30/3581 (0.8)	1.03 (0.62, 1.72)
142	**22**/2014 (1.1)	**41**/2040 (2.0)	**1.87** (1.11, 3.14)
174	2/81 (2.5)	6/163 (3.7)	1.55 (0.31, 7.69)
Meta (337, 142)	51/5590 (0.9)	71/5621 (1.3)	1.39 (0.97, 2.00)
Meta (337, 142, 174)	53/5671 (0.9)	77/5784 (1.3)	1.40 (0.99, 1.99)

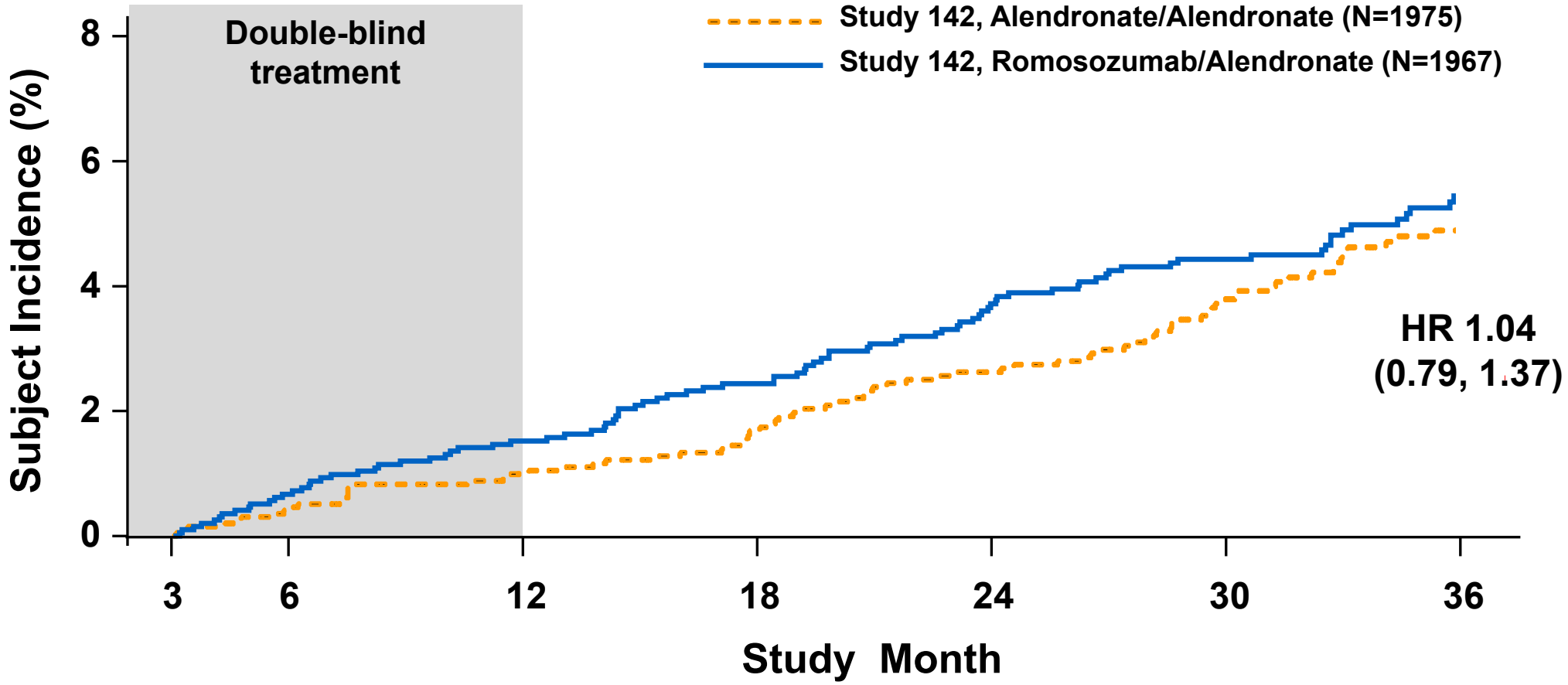


Study 142: Excess Number of Events (95% CI) per 1000 Patients Treated



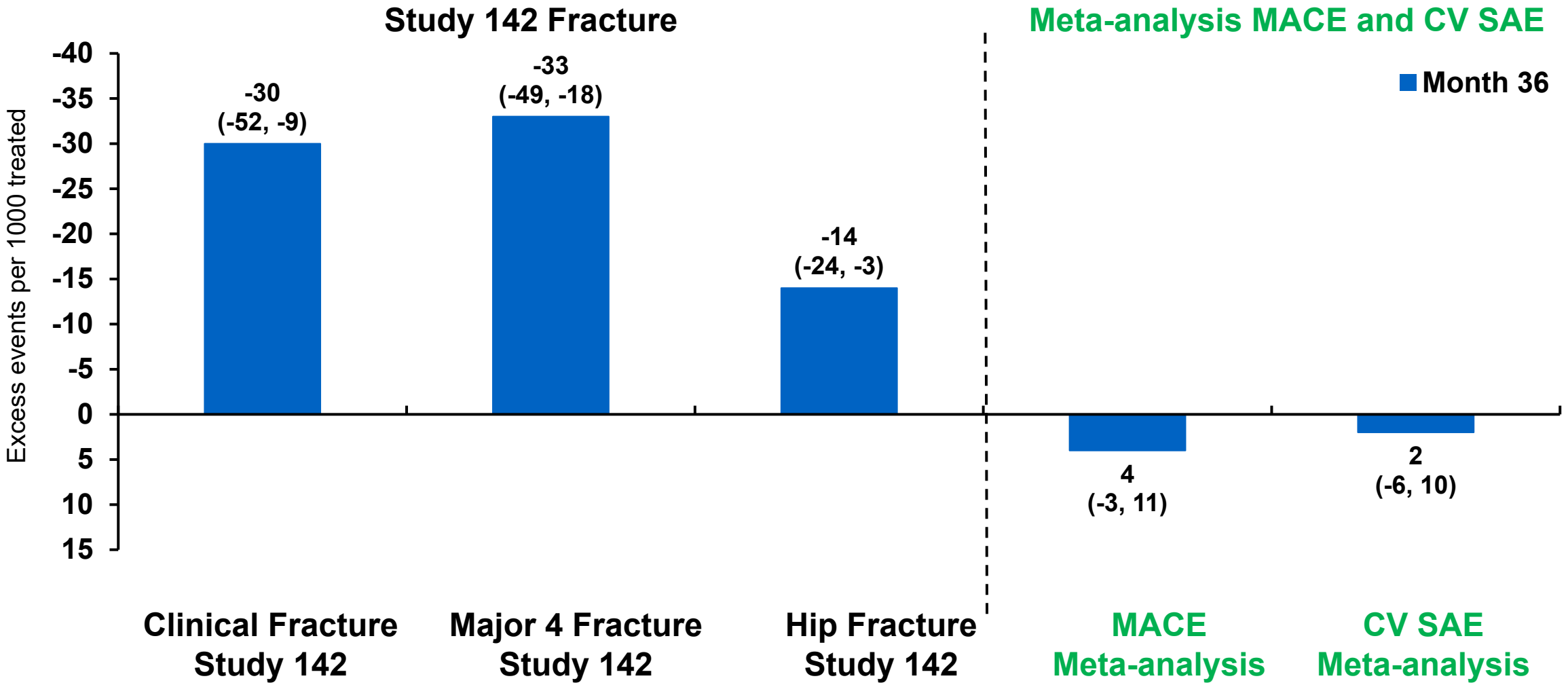
Major 4 fractures are composite of hip, pelvis, humerus, or clinical vertebral fracture.

Study 142: Landmark Analysis Starting at 3 Months: Time to First MACE



N = Number of subjects who received at least 1 dose of investigational product in the 12-month double-blind period
n = Number of subjects at risk for event at time point of interest

Study 142 and Meta-analysis: Excess Number of Events (95% CI) per 1000 Patients Treated



Major 4 fractures are composite of hip, pelvis, humerus, or clinical vertebral fracture.